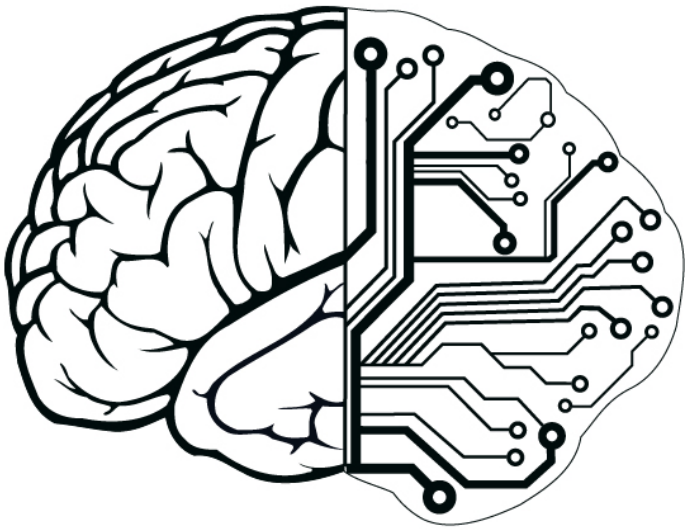
DISS. ETH NO. 23313

IMPROVING HOSPITAL DRUG SAFETY

IDENTIFICATION OF MEDICATION ERRORS AND SUBSEQUENT DEVELOPMENT, IMPLEMENTATION AND OUTCOME EVALUATION OF ALERT ALGORITHMS FOR THEIR TARGETED PREVENTION



DAVID FRANKLIN NIEDRIG

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IDENTIFICATION OF MEDICATION ERRORS AND SUBSEQUENT DEVELOPMENT, IMPLEMENTATION AND OUTCOME EVALUATION OF ALERT ALGORITHMS FOR THEIR TARGETED PREVENTION

A thesis submitted to attain the degree of
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Table of Contents

1. Summary

Any drug prescription requires careful weighting of risks vs. benefits. Failure to do so or to ignore known contraindications, recommended dose-adjustments and other precautions represents a medication error that may result in adverse drug events, i.e. harm to the patient. Clinical decision support systems can routinely detect potential medication errors and issue automated alerts for their prevention. However, current systems typically focus on high sensitivity at the price of low specificity regarding relevance of their alerts. In clinical practice this results in an excessive number of alerts to prescribers with subsequent alert fatigue and indiscriminate alert overriding, i.e. even important warnings are ignored. So medication errors continue to be a theoretically avoidable yet persistent burden for healthcare systems and patients. Therefore this thesis pursued the following objectives:

I) Systematic quantification of potential medication errors in a real-life hospital setting.
II) Validation of the clinical relevance of selected potential medication errors and associated adverse events.
III) Development, implementation and outcome assessment not only of highly sensitive but also of highly specific alert algorithms for the prevention of clinically relevant medication errors.

I) Two studies were performed in order to systematically quantify potential medication errors:
A local pharmacoepidemiological database including 6.6 million drug administrations during approximately 82000 hospitalizations was successfully developed based on raw data extracted from the electronic medical records system of a tertiary care hospital. After its validation, highly efficient algorithms were developed that identified potential medication errors. They allowed the retrospective assessment of a considerable number of contraindicated and/or critical prescriptions. Sensitivity and specificity regarding clinical relevance of these potential medication errors was enhanced by the use of additional patient-specific laboratory data and repeated clinical validation procedures.
With the help of a newly developed interface with ID PHARMA CHECK® - a commercially available clinical decision support system - several ten thousand potential drug interactions, contraindications and dosing errors were identified and assigned to formal severity categories. 48 distinct contraindicated drug interactions

were considered as clinically relevant and suitable for display of highly specific alerts within a clinical information systems; 32 alert algorithms required retrieval and implementation of current patient-specific information such as laboratory results in order to reach high specificity. The resulting algorithms were subsequently programmed for routine use with the clinical decision support system.

II) Three sub-studies were conducted within the pharmacoepidemiological database and addressed specific safety concerns of pharmacotherapy in clinical practice:
The first of these studies identified 1136 hospitalizations with exposure to second-generation antipsychotics. Blood pressure, blood glucose, lipids and body mass index should be routinely monitored in those patients, however they were found to be documented in 97.7, 75.7, 24.6 and 77.4 % of hospitalizations, respectively. 63.4, 70.8 and 37.1% of the patients with hyperglycemia, dyslipidemia and hypertension, respectively, had no pharmacotherapy for these conditions. Among patients exposed to second-generation antipsychotics and concomitant use of drugs featuring a high risk for potentially severe adverse drug events, one case with associated neutropenia and four cases with abnormal QTc-interval were detected. Specific monitoring for such adverse drug events was not performed in 89.8% of patients with related high-risk drug combinations.
The second sub-study analyzed the use of benzodiazepines (including “Z-drugs”) that were found to be administered to 48.3% of 53081 patients hospitalized in 2011 and 2012. Validated algorithms identified 3372 patient-days (2.9%) with comedication that significantly inhibits the respective benzodiazepines’ metabolism. Validation revealed 205 cases with clinically relevant medication errors. Among those, 23 cases with associated adverse drug events such as severe CNS-depression, falls with subsequent injuries and severe dyspnea were detected.
The third sub-study analyzed 3444 hospitalizations with administrations of selected macrolide and quinolone antibiotics and identified concomitant use of additional QT-prolonging drugs in 1332 (38.7%). Among those we identified 7 events of related QTc-prolongation, but 50.4 % had no ECG-monitoring. Of all patients exposed to the studied antibiotics 547 (15.9%) featured episodes of hypokalemia, an important additional risk factor for potentially lethal Torsade de Pointes arrhythmia. Clinically relevant QT-prolongation was detected in 7 patients. Another 31 patients were exposed to contraindicated comedication with simvastatin, atorvastatin or tizanidine where the risk of pharmacokinetic drug-drug interactions clearly outweighed benefits, 3 thereof with associated adverse events.

III) These two studies then aimed to develop new solutions for the prevention of such avoidable potential medication errors and associated adverse drug events:
According to our pharmacoepidemiological database overdosing of paracetamol occurred in 988 hospitalizations per year, but in only 11 (0.4 %) this was judged as clinically relevant (≥ 5 g on ≥ 3 consecutive days). A new alert algorithm was developed as part of this study, and in 2014 it was implemented into the hospital-wide electronic drug prescribing system. It automatically detects cases of paracetamol overdosing, and after manual assessment alerts were issued in 23 cases, with subsequent changes to prescriptions in 21 (91.3 %) thereof. While the occurrence of mild and therefore clinically irrelevant acetaminophen overdosing changed only marginally in 2014 (n = 914), no clinically relevant overdosing occurred anymore.
The second automated alert concerned metformin overdosing in renal impairment. It has been used in routine clinical practice for three years and generated 2145 automated alerts (about 2 per day). Validated expert recommendations regarding metformin therapy, i.e. dose reduction or stop, were issued for 381 patients (about 3 per week). Follow-up was available for 240 cases, and prescribers' compliance with recommendations was 79 %. Furthermore, during 3 years we identified 8 local cases of lactic acidosis associated with metformin therapy in renal impairment that could not be prevented, e.g. because metformin overdosing had occurred before hospitalization.

Besides these principal studies, spontaneous reports from international pharmacovigilance databases on liver disease associated with the new oral anticoagulant rivaroxaban and allergy-like reactions to herbal medicines were analyzed in two additional studies.

In conclusion, local pharmacoepidemiological databases can be created using already available electronic medical information systems. They are an innovative and promising new approach for the identification and management of medication errors and resulting adverse drug events. Such databases are able to quantify clinically relevant medication errors and thereby provide data for a rational selection of targets for new and highly specific preventive safety measures. Any such measures must be integrated into a comprehensive hospital safety concept where local drug safety experts play an important role for the evaluation and communication of medication errors. Within such a system, automated alert algorithms that use also patient-specific information are a cornerstone for the proactive prevention of medication errors and resulting adverse drug events.

Zusammenfassung

Bei der Verordnung eines Arzneimittels sollten stets dessen Risiken und Nutzen gegeneinander abgewogen werden. Wird dies nicht gemacht, oder werden bekannte Kontraindikationen, empfohlene Dosis-Anpassungen und andere Vorsichtsmassnahmen nicht berücksichtigt, stellt dies einen Medikationsfehler dar. Dieser kann zu einer unerwünschten Arzneimittelwirkung führen und dem Patienten schaden. Software zur Unterstützung klinischer Entscheidungen kann standardmässig potentielle Medikationsfehler identifizieren und automatisch Warnmeldungen zu deren Verhinderung auslösen. Derzeit fokussieren solche Systeme auf hohe Sensitivität, was eine geringe Spezifität bezüglich der klinischen Relevanz der Warnmeldungen zur Folge hat. Im klinischen Alltag hat dies eine übermässige Anzahl Warnungen zur Folge, welche zu einer Abstumpfung (*alert fatigue*) der Verschreiber führt. Schliesslich werden alle Warnmeldungen komplett übergangen und somit auch wichtige Hinweise ignoriert. Daher sind Medikationsfehler noch immer eine nur theoretisch vermeidbare und in der Praxis weiterhin bestehende Belastung für das Gesundheitswesen und die betroffenen Patienten. Daraus leiteten sich folgende Ziele für diese Doktorarbeit ab:

I) Die systematische Quantifizierung von potentiellen Medikationsfehlern welche sich im praktischen Alltag eines Spitals ereignen.
II) Die Validierung der klinischen Relevanz von ausgewählten potentiellen Medikationsfehlern und damit assoziierten unerwünschten Arzneimittelwirkungen.
III) Die Entwicklung, Implementierung und Auswertung von sowohl hochsensitiven als auch hochspezifischen Warn-Algorithmen zur Verhinderung von klinisch relevanten Medikationsfehlern.

I) Die zwei ersten Studien dienten der Analyse potentieller Medikationsfehler:
Aus Rohdaten, welche aus dem klinischen Informationssystem eines Tertiärspitals extrahiert wurden, konnte eine lokale, validierte, pharmakoepidemiologische Datenbank erstellt werden. Diese enthält ca. 6.6 Millionen Arzneimittelverabreichungen verteilt auf rund 82000 Hospitalisierungen. Es wurden hocheffiziente Algorithmen entwickelt, welche eine beachtliche Anzahl potentieller Medikationsfehler identifizierten. Darunter fanden sich zahlreiche übergangene Kontraindikationen und andere kritische Verordnungen aus dem klinischen Alltag. Die Sensitivität und Spezifität bezüglich der Detektion von klinisch relevanten

Medikationsfehlern wurde durch wiederholte Validierungsprozesse erhöht und durch die zusätzliche Verwendung patientenspezifischer Laborwerte weiter gesteigert.
Mit Hilfe einer neu entwickelten Schnittstelle zu ID PHARMA CHECK® - einer kommerziellen Software zur Unterstützung klinischer Entscheidungen - konnten anhand einer Massenanalyse mehrere Zehntausend potentiell gefährliche Arzneimittelinteraktionen, Kontraindikationen und Dosierungsfehler identifiziert und in formale Gefahren-Kategorien eingeteilt werden. Davon wurden bislang 48 verschiedene kontraindizierte Arzneimittelinteraktionen als klinisch relevant beurteilt und als passend für eine aktive Warnung befunden. Weitere 32 Warn-Algorithmen benötigten die Berücksichtigung von aktuellen patientenspezifischen Informationen, z.B. Laborwerte, um eine hohe Spezifität zu erreichen. Diese Algorithmen wurden daraufhin zum routinemässigen Gebrauch in die Software einprogrammiert und werden jetzt im klinischen Alltag eingesetzt.

II) Mit der pharmakoepidemiologischen Datenbank wurden daraufhin drei Sub-Studien durchgeführt, welche sich spezifischen Fragestellungen zur Arzneimittelsicherheit im klinischen Alltag widmeten:
Die erste solche Untersuchung analysierte 1136 Hospitalisierungen bei denen atypische Neuroleptika eingesetzt wurden. Bei diesen Patienten sollten Blutdruck, Blutzucker, Lipidstoffwechsel und der Body-Mass-Index routinemässig überwacht werden. Dies war jedoch nur in 97.7, 75.7, 24.6 und 77.4 % der Hospitalisierungen der Fall. Patienten welche an Bluthochdruck, Hyperglykämie oder Dyslipidämie litten erhielten in 63.4, 70,8 und 37.1 % der Fälle keine entsprechende Pharmakotherapie. Unter den Patienten, welche zu den atypischen Neuroleptika zeitgleich weitere Arzneimittel erhielten, die zusammen zu potentiell schweren Nebenwirkungen führen können, wurden ein Fall mit assoziierter Neutropenie und vier Fälle mit abnormalem QTc-Intervall entdeckt. Eine spezifische Überwachung bezüglich solcher unerwünschten Arzneimittelwirkungen wurde in 89.9 % der Fälle mit hochriskanter Co-Medikation nicht durchgeführt.
Eine zweite Sub-Studie analysierte den Gebrauch von Benzodiazepinen (inklusive der sogenannten Z-Wirkstoffe), welche bei 48.3 % der 53081 Patienten angewendet wurden, welche 2011 und 2012 hospitalisiert waren. Validierte Algorithmen infizierten 3372 Patiententage (2.9%) mit einer Co-Medikation, welche den Metabolismus der entsprechenden Benzodiazepine erheblich beeinträchtigten. Deren Validierung zeigte 205 Fälle mit klinisch relevanten Medikationsfehlern, welche in 23 Fällen mit assoziierten unerwünschten Arzneimittelwirkungen, darunter ausgeprägte ZNS-Dämpfung, Stürze mit Verletzungen und Atemstillstand.

Die dritte Sub-Studie untersuchte 3444 Hospitalisierungen mit Verabreichungen von ausgewählten Makrolid- und Chinolon-Antibiotika und ergab eine zeitgleiche Anwendung weiterer QT-verlängernder Wirkstoffe bei 1332 (38.7 %) davon. Dabei fand bei 50.4 % keine EKG-Überwachung statt. Bei 15.9 % traten Hypokaliämien auf, ein wichtiger und vermeidbarer Risikofaktor für potentiell tödliche Torsade de Pointes Arrhythmien. Eine klinisch relevante QT-Verlängerung wurde bei 7 Patienten festgestellt. Bei weiteren 31 Patienten wurden die untersuchten Antibiotika zeitgleich mit Simvastatin, Atorvastatin oder Tizanidin verabreicht. Aufgrund von ausgeprägten pharmakokinetischen Wechselwirkungen übersteigen dabei die Risiken klar jeden Nutzen. Bei 3 dieser Patienten wurden assoziierte unerwünschte Arzneimittelwirkungen festgestellt.

III) Zwei weitere Studien widmeten sich danach der Entwicklung neuer Lösungsansätze zur Verhinderung solcher potentieller Medikationsfehler und den damit assoziierten unerwünschten Arzneimittelwirkungen:
Gemäss der verwendeten pharmakoepidemiologischen Datenbank wird jährlich bei 988 Hospitalisierungen Paracetamol überdosiert. Dies wurde jedoch nur in 11 (0.4 %) Fällen als klinisch relevant (≥ 5 g / d für ≥ 3 aufeinander folgende Tage) eingestuft. Ein neuer Warn-Algorithmus wurde für diese Studie entwickelt und 2014 in das spitalweite elektronische Verordnungssystem implementiert. Dieser detektiert Paracetamol-Überdosierungen, welche nach einer manuellen Evaluation durch lokale Experten für Arzneimittelsicherheit in 23 Fällen an die verschreibenden Ärzte weitergeleitet wurden. Diese änderten die Paracetamol-Verordnungen in 21 Fällen (91.3 %). Währen sich die Anzahl klinisch irrelevanter, moderater Paracetamol-Überdosierungen 2014 nicht veränderte, fanden keine klinisch relevanten Überdosierungen mehr statt.
Der zweite automatisierte Warn-Algorithmus zielte auf Metformin-Überdosierungen bei Patienten mit eingeschränkter Nierenfunktion ab. In den 3 Jahren seit der Implementierung 2012 generierte ein Screening-Algorithmus 2145 Warnmeldungen an lokale Experten für Arzneimittelsicherheit (ca. 2 pro Tag). Nach deren Evaluation wurden in 381 Fällen spezifische Empfehlungen zur Dosisanpassung (Reduktion oder Stopp) an die verschreibenden Ärzte weitergeleitet (ca. 3 pro Woche). Für 240 Fälle standen Informationen für weitere Auswertungen zur Verfügung wobei bei 79.3 % davon die Empfehlungen umgesetzt wurden. Innerhalb dieser 3 Jahre wurden 8 Patienten mit Metformin-assoziierter Laktatazidose identifiziert. Diese ereigneten sich jedoch in Situationen, in denen eine zeitnahe Warnung nicht möglich war, z.B. weil Metformin schon vor Spitaleintritt überdosiert worden war.

Zwei zusätzliche Studien widmeten sich nebenher der Analyse von Spontanmeldungen aus internationalen Pharmakovigilanzsystemen. Dabei wurden Leberschäden, welche mit dem Gebrauch des neuen oralen Antikoagulans Rivaroxaban assoziiert waren, sowie allergie-ähnliche Reaktionen auf Phytotherapeutika untersucht.

Folgende Schlussfolgerungen können gezogen werden: Bereits bestehende elektronische Verordnungssysteme ermöglichen die Erstellung lokaler pharmakoepidemiologischer Datenbanken. Diese ermöglichen einen neuartigen und innovativen Ansatz zur Identifikation und Verhinderung von Medikationsfehlern und damit assoziierten unerwünschten Arzneimittelwirkungen. Solche Datenbanken erlauben die Quantifizierung von klinisch relevanten Medikationsfehlern. Dies kann die Basis für eine rationale Auswahl von Zielen darstellen, anhand derer hochspezifische Präventivmassnahmen entwickelt werden können. Jede solche Massnahme muss in ein umfassendes Spital-Sicherheitskonzept eingebettet werden, in dem lokale Experten für Arzneimittelsicherheit eine tragende Rolle bei der Kommunikation und Verhinderung von Medikationsfehlern spielen. Innerhalb eines solchen proaktiven Systems können automatisierte Warn-Algorithmen, welche patientenspezifische Informationen berücksichtigen, einen fundamentalen Beitrag zur Verhinderung von Medikationsfehlern und daraus resultierten unerwünschten Arzneimittelwirkungen leisten.

2. Background, Current State of Research and Principal Methods

2.1. Drug Safety and Adverse Drug Events

For any drug with granted marketing authorization its label, i.e. its approved indication and usage, is initially based on the properties that have been previously assessed in clinical trials, i.e. ‘premarketing’ data. By administering a drug according to its label, clinicians and patients can expect benefits to usually outweigh currently known potential risks. Nevertheless, using a drug not in accordance with its label is common in clinical practice and may indeed be unavoidable. Sometimes even the use in spite of explicit contraindications may be justifiable. In these situations prescribers must carefully assess the risks for adverse drug events (ADE), monitor the patient’s reactions to the drug and consider therapeutic alternatives.

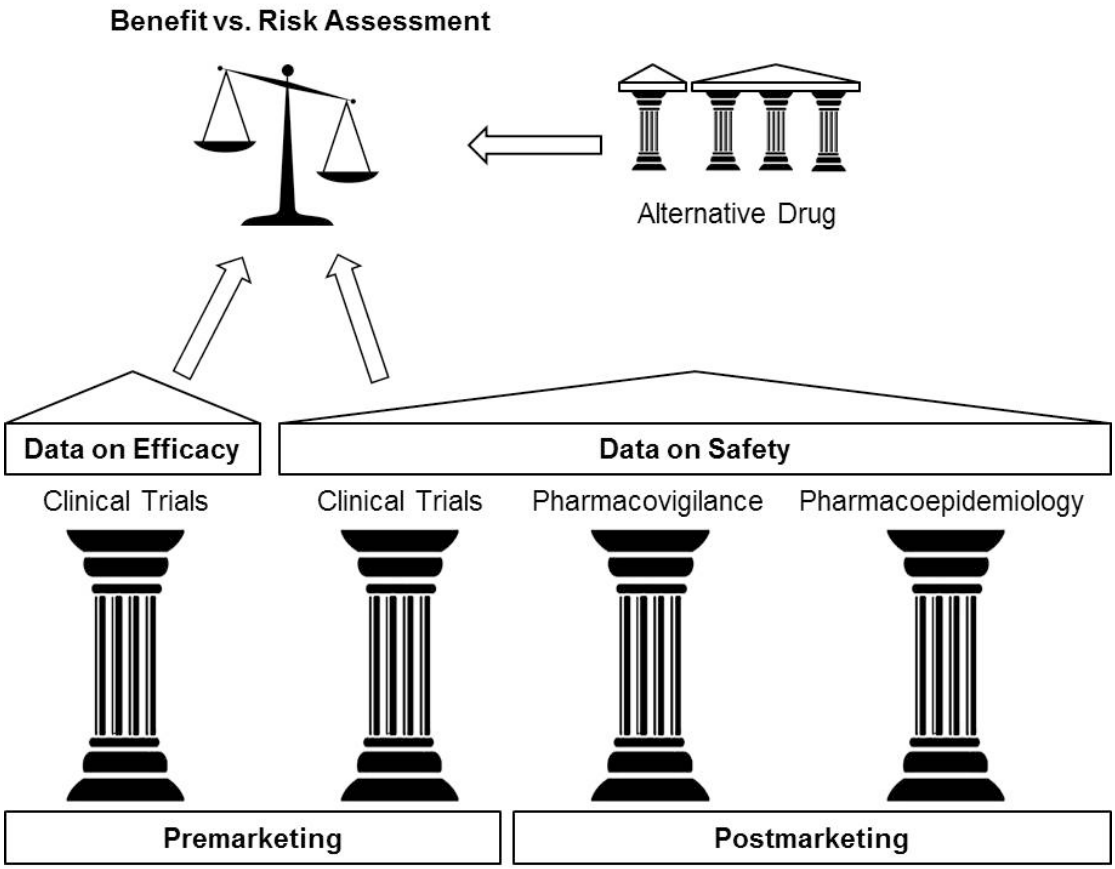


Figure 1: Integrative Assessment of Clinical Drug Safety Based on Available Data from Different Sources, adapted from: Arzneimitteltherapie, Wirksamkeit - Sicherheit - Praktische Anwendung, page 28.

Due to their high costs studies that provide the evidence for granting marketing authorization are limited in size and scope and often only include a few hundred or thousand usually highly selected patients, which are not necessarily representative of the population that will receive the drug after market approval. Therefore some risks such as delayed or rare ADE or potentially dangerous drug-drug interactions (DDI) are often not detected before the drug is widely used in clinical practice. Approximately 80% of all ADE can be classified as “Type-A” ADE or ‘augmented effects’. These ADE are typically dose-dependent and can be explained by the pharmacological properties of the drug and typically affect particular organs. Such ADE usually cease after dose reduction or drug withdrawal and are reproducible in individual patients. Type A ADE are preventable and represent a well-known risk that can be managed accordingly, e.g. by choosing another drug with a different mode of action or by careful dose-titration. Type-B ADE or ‘bizarre effects’ on the other hand are unexpected and rare reactions. They are often caused by immunological reactions to a drug and may be associated with previous exposure to similar drugs. In Type-B ADE even low doses of a drug can affect multiple organs and lead to severe complications. Type-B ADE are sometimes also referred to as ‘idiosyncratic ADE’ and are usually not predictable and therefore difficult to prevent. Additional classifications for ADE have been proposed such as Type C for ‘chronic effects’, Type D for ‘delayed’ effects, Type E for ‘end of treatment effects’ and Type F for ‘failure of therapy’. Other classifications, e.g. according to affected organs or severity of the adverse event are also applied. Idiosyncratic adverse drug events are usually not preventable, and such non-preventable adverse drug events are designated adverse drug reactions (ADR).[1] The WHO definition of ADR from 1972 differs from this definition as it does not relate to the preventability of an adverse event, but to the presence of a suspected causal relationship between a drug and an adverse event. The WHO definition will not be used in this thesis - with exception of the study on herbal drugs which exclusively used data from the WHO pharmacovigilance database.[2,3]

2.1.1. Detection and Quantification of Adverse Drug Events

There are three different principal sources of information to detect ADE: clinical trials, individual cases as reported to and collected in pharmacovigilance systems and pharmacoepidemiological studies (see also Figure 1).[3] Each source has its inherent strengths and limitations.

Clinical trials have major limitations mentioned above, but their typical strengths include the quantification of absolute and relative risks of frequent ADE.

In the postmarketing phase spontaneous reports to pharmacovigilance systems allow the identification of rare ADE and are important for the generation of safety signals that may warrant increased surveillance or further studies. If an ADE is observed and a causal relationship to a recently administered drug is suspected, it must be reported to pharmacovigilance systems. Certain ADE are of special interest, e.g. those that are life-threatening, causing permanent harm or leading to otherwise clinically relevant consequences. In order to evaluate whether a drug is responsible for an observed adverse event, ADE reported to pharmacovigilance-systems are subject to a standardized causality assessment as defined by the WHO applying a semi-quantitative categorization, i.e. the criteria of the Council for International Organizations of Medical Sciences CIOMS.[2] Because of the unknown number of exposed patients and the unknown true number of ADE (due to underreporting),an exact quantification of the risk for an ADE is not possible based on pharmacovigilance data.

Pharmacoepidemiological studies can provide a reliable quantitative assessment of a drugs' risks and benefits representative of real-life settings. Due to the lack of randomized treatment assignment their biggest challenge is the control of confounding, but sophisticated study designs and data analysis techniques can minimize the influence of potential confounders. Pharmacoepidemiological studies complement the other sources of information in drug safety by allowing quantitative analyses of potential safety-issues that could not be studied in clinical trials due to ethical or financial restrictions.

Once an ADE is established as a previously unknown or underestimated risk associated with the use of a drug, changes to its label may be required or the drug may even be withdrawn from the market.[3]

2.2. Medication Errors, Adverse Drug Events and Risk Factors

Any failures in the drug treatment process that may lead to harm to the patient are designated as medication errors (ME).[4] They represent the most common preventable cause for ADE and are a major public health burden. While mistakes regarding storing and preparation of drugs are also considered ME, errors during the prescription or administration process account for about 90% of preventable ADE.[5,6] Inadequate prescriptions, i.e. with risks clearly exceeding benefits, are of special interest: these decision-based ME are theoretically preventable by automated alerts that trigger upon ordering of the medication. For the studies subsequently presented in this thesis, a ME is primarily considered any drug prescription or administration featuring an unfavorable benefit-risk situation. While it is usually difficult to predict the risk for Type B ADE, there are well-established risk factors for more frequent Type A ADE and it is easier to quantify the risks of most potential ME. Being dose dependent, Type A ADE are more common in patients continuously exposed to the responsible drug or in situations where unintentionally high drug concentrations are achieved. Such overdosing may result from:

- Reduced drug clearance without accordingly reduced dosing, e.g. in patients with renal- or hepatic failure.
- Exposure to pharmacokinetic DDI that significantly reduce the enzymatic metabolism of certain drugs.
- Known genetic polymorphisms that affect patients' metabolic capacity, i.e. slow metabolizers for which certain drugs' dosing need to be carefully titrated.

Additionally, pharmacodynamic DDI can increase the risk for Type A ADE, e.g. by synergistic modes of action that result in an increased overall toxicity for certain organs. Further risk factors for ADE may not be directly responsible for the development of an ADE but are strongly associated with the previously mentioned factors, e.g. high age, polymorbidity and pronounced polypharmacy. They can also predispose to more severe outcomes of an ADE and are characteristic for frail patients in whom an especially careful benefit-risk assessment is warranted.
Any ADE that results from DDI or lack of dose adjustments denotes a ME that is clinically relevant and therefore represents a suitable target for preventive countermeasures such as automated alerts.[3]

2.2.1. Applying Pharmacovigilance and Pharmacoepidemiology

The distinction of clinically relevant 'true' from irrelevant 'formal' ME remains a major challenge. 'True ME' have a high risk to harm patients, whereas in case of only 'formal ME' a drug may not be used according to its label, but the risk for an ADE is acceptable as compared to the drug's benefits. However this discrimination is crucial if efficient preventive measures are to be developed and implemented. And while the presence some patient-related risk factors for an ADE can be easily identified and may therefore be used systematically to assess the clinical relevance of a ME, there are other important circumstances that need to be considered as well in order to validate a potential ME:

- Prescribers may carefully monitor drug levels or the patients' reactions.
- Exceedingly high doses are administered in patients with established poor drug absorption or genetically determined ultra-fast metabolism.
- Ongoing use of drugs only intended for short-term administration may be preferable to applying drugs from other classes that are not well tolerated in certain patients
- Drugs and doses may be used in palliative situations when their benefits categorically outweigh any risks.

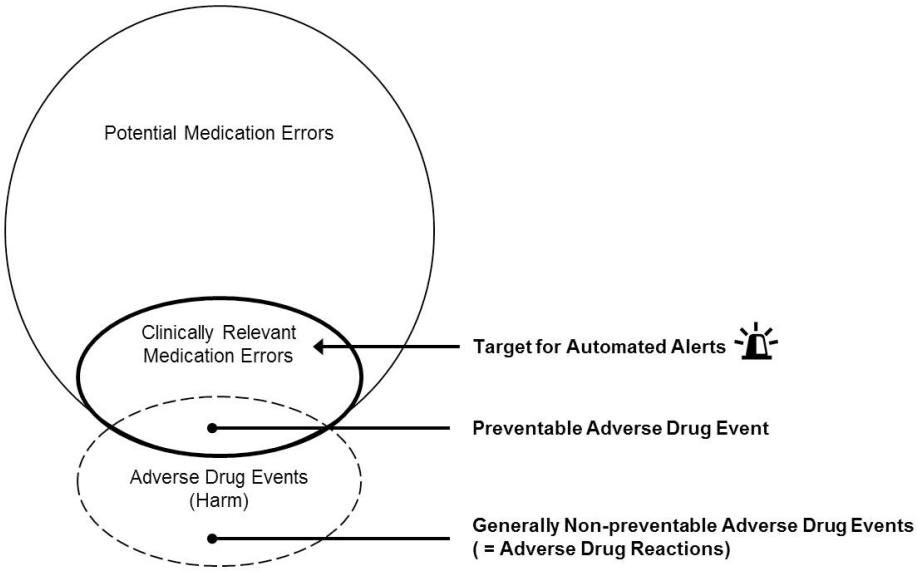


Figure 2: Potential and Relevant Medication Errors, Preventable and Generally Non-preventable Adverse Reactions and Intercepted Errors. Modified according to: Preventing Medication Errors: Quality Chasm Series, The National Academic Press 2007, page 36.

In order to quantify potential and true ME, their relevance can be validated in the individual clinical context by applying concepts and methods from pharmacoepidemiology and pharmacovigilance. These methods allow the identification of validated ME, e.g. by using administrations of highly specific antidotes as a marker for cases with manifest drug-related ADE. Cohort studies can provide the absolute number of patients exposed to ME, with and without consideration of relevant risk factors. Formal causality assessment on a case-by-case basis according to the WHO / CIOMS criteria is an important tool to prevent overestimation of the relevance of ME and concurrently manifest adverse events by excluding ADE that are not primarily related to a ME but were unavoidable, i.e. an ADR. In the context of this thesis and the therein-presented studies, 'clinically relevant ME' refers to ME that have management implications, i.e. that the responsible prescriber would need to take an action because the ME has a relevant potential for harming the patient as compared to the benefits of the assessed medication.

2.2.2. Medication Errors in Hospitals: Common

The internationally renowned, government-independent non-profit Institute of Medicine (IOM) in the USA published a comprehensive report on medication errors in 2006. It defines medication error as "any error occurring in the medication-use process. Examples include wrong dosage prescribed, wrong dosage administered for a correctly prescribed medication, or failure to give (by the provider) or take (by the patient) a medication".[1] The IOM estimates that on average, hospitalized patients are exposed to at least one ME per day, which they deem a conservative assessment subject to considerable variation depending on the studied institution and applied criteria. According to the IOM, ME occur most frequently upon prescription and administration but can also concern drug dispensing or inadequate monitoring of the patient's response to the drug. Also the lack of prescribing drugs known to be effective in patients with established conditions (e.g. heart failure) are known medication errors. Insufficient prophylaxis against infections or thrombosis can also be considered a ME in hospitalized patients. Data published from a survey representative for the Swiss general population from 2011 revealed that approximately 5 % were exposed to a ME in the last year. Regarding medical errors, 33 % of the patients indicated that the incidence occurred during a hospitalization. Length of hospital stay, has been found to be associated with the exposure to these

self-reported medical errors.[7] Evidence from studies performed in Swedish and Spanish hospitals indicates that
30 % and 37 % of the adverse events in hospitals are caused by the patients' medication, and that of those 27 % and 35 %, respectively, could have been prevented.[8,9] In the setting of a tertiary care hospital exposure to potential ME is likely higher compared to primary care: risk factors such as polymorbidity and subsequent polypharmacy are very common. In addition, prescribers are working in highly specialized units that are often unfamiliar with drugs prescribed by other specialists. The Swiss Federal Office of Public Health published a fact sheet in 2015 that confirmed that ME are a major concern for patient safety and that they occur especially frequent upon hospital admission and discharge.[10] Finally, the "incidence of ME varies substantially depending on the clinics: they are much more frequent in intensive care units, for example, where patients receive an average of 25 medications per day, and much less of a problem in areas such as obstetrics, where medications are generally avoided."(Bates and Slight 2014).[11]

2.2.3. Medication Errors in Hospitals: Expensive

As with any health-related costs, it is challenging to assess the financial impact of ME in hospitals. Additional in-hospital costs have been estimated to amount to approximately $ 3000 - $ 6000 for a preventable ADE, a figure which is based on US healthcare data from 1993 and only includes costs occurring in the hospital[12,13] A more recent study using an advanced methodology and data from 2005 and 2006 basically confirmed these findings with estimated incremental treatment costs of approximately $ 8500 per ME. Data from Swiss studies suggests yearly costs of 70 - 100 millions due to ME.[14] Similar to the incidence of ME, the related costs of ME may vary greatly, depending on the studied setting: a recent study performed in patients with kidney transplants reveal median incremental costs consequent to ME of approximately $ 18000 with an interquartile range of approximately
$ 3000 - $ 56000.[15]

2.2.4. Medication Errors in Hospitals: Harmful

Although potential ME are common, most of them do not result in harm. However those ME that cause ADE in hospitalized patients frequently occur at the prescribing or administering stages,[11] such as potentially avoidable DDI that are responsible for 5 - 26 % of the observed ADE in hospitals.[16-18] The IOM has estimated that ME cause one of 131 outpatient and one of 854 inpatient deaths.[19] Approximately 1 - 7 % of the patients exposed to ME have been identified to experience an associated ADE.[12,20,21] Further studies from the Netherlands have assessed medication as cause of permanent injury or death in 2.6 - 10.5 %.[22]

In clinical practice ME related to DDI may often not be recognized as a cause for an ADE, subsequently leading to an underestimation of ME-associated harm. Additionally, overseeing a ME as a cause of or significant contributor to an ADE may trigger a prescription cascade: signs and symptoms of an ADE that is not recognized as such are treated with another drug that also has the potential to cause DDI and further or even more severe ADE.[23]

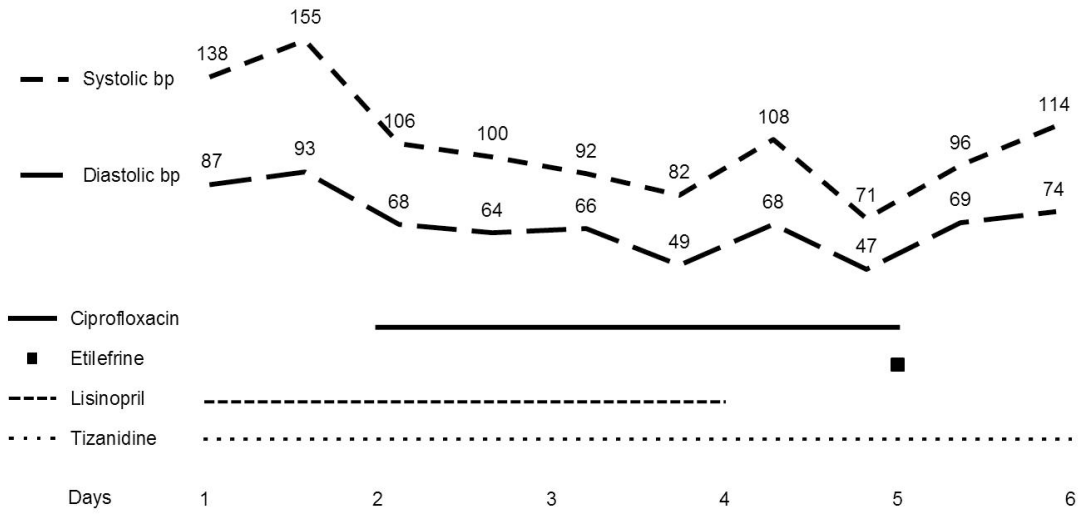


Figure 3: Example for a Preventable ME that Caused an ADE as Detected in the Study Presented in section 3.5., i.e. Drug Safety of Macrolide and Quinolone Antibiotics in a Tertiary Care Hospital: Administration of Contraindicated Comedication and QT-Prolongation.
The patient received the antibiotic drug ciprofloxacin on day 2 in addition to his current medication. Through a pharmacokinetic drug-drug interaction the muscle-relaxing drug tizanidine accumulated, causing pronounced hypotension (nadir systolic / diastolic blood pressure: 71 / 47 mmHg), with nausea, severe dizziness and fatigue. Instead of replacing, reducing or stopping tizanidine, the prescribers first stopped the antihypertensive therapy with lisinopril and then prescribed etilefrine, a sympathomimetic drug to treat the ADE. Fortunately the patient recovered without experiencing permanent harm. Figure adapted from the poster presented at the GSASA congress 2015 in Zurich.

2.3. Computerized Physician Order Entry

Clinical information systems (CIS) may electronically document any information related to hospitalized patients including administrative information, lab data, prescribed and administered drugs, results from imaging procedures and admission- and discharge reports. All this information can be displayed in an electronic medical record. As an integral part of any CIS, computerized physician order entry (CPOE) systems principally refer to electronic prescription software. The abbreviation CPOE is sometimes also used as abbreviation for computerized provider order entry, since these systems may allow non-physicians to enter orders and usually are also used to record drug administrations and other procedures by additional caregivers.
Compared to paper-based prescription, introduction of a CPOE has been shown to dramatically reduce certain ME, e.g. transcription errors, with an overall reduction of all ME by approximately 50 %.[24] Results from any such assessment greatly depend on the parameters that defined the baseline for ME and need to be viewed in their methodological and institutional context. Some studies also found CPOE to allow or even promote new and potentially dangerous ME.[6,25]
Besides the obvious advantages of CPOE in clinical practice, they can provide a database for highly efficient evaluations of prescription patterns, quality controls and many other automated administrative, logistic or financial analyses.
Based on survey-data from 2011 that was published in 2013, approximately 40% of the Swiss hospitals used CPOE.[5]

2.3.1. Clinical Decision Support Systems

Clinical decision support systems (CDSS) may be defined as: “knowledge software designed to support clinical processes by linking patient data with medical and / or drug-specific knowledge and to provide advice for healthcare professionals while diagnosing, treating or monitoring patients” (Carli-Ghabarou et. al. 2013).[5] The information processed by CDSS may come from many different subsystems of a CIS: lab data, drug prescriptions and actual administrations, diagnoses, vital parameters such as blood pressure or heart rate and any other information that can be documented in a standardized structured way, i.e. not as free text or images, but in pre-defined terms. Considering that much of this information may constantly change during a hospitalization, quality and timeliness of the data is essential for providing reliable, useful and comprehensive decision support.[26]

Approximately half of the hospitals that feature CPOE also use integrated CDSS, i.e. 20% of all hospitals, as assessed in 2011.[5] Among these CDSS, most provided passive, i.e. on-demand or non-interruptive, decision support for pairwise drug-drug interactions (DDI), pre-set protocols to facilitate prescriptions of common drug combinations and provided information on the hospital formulary. Despite the potential for a multitude of comprehensive preventive alerts, only a very limited fraction of the available patient-related data was used by the CDSS to prevent ME.[5]

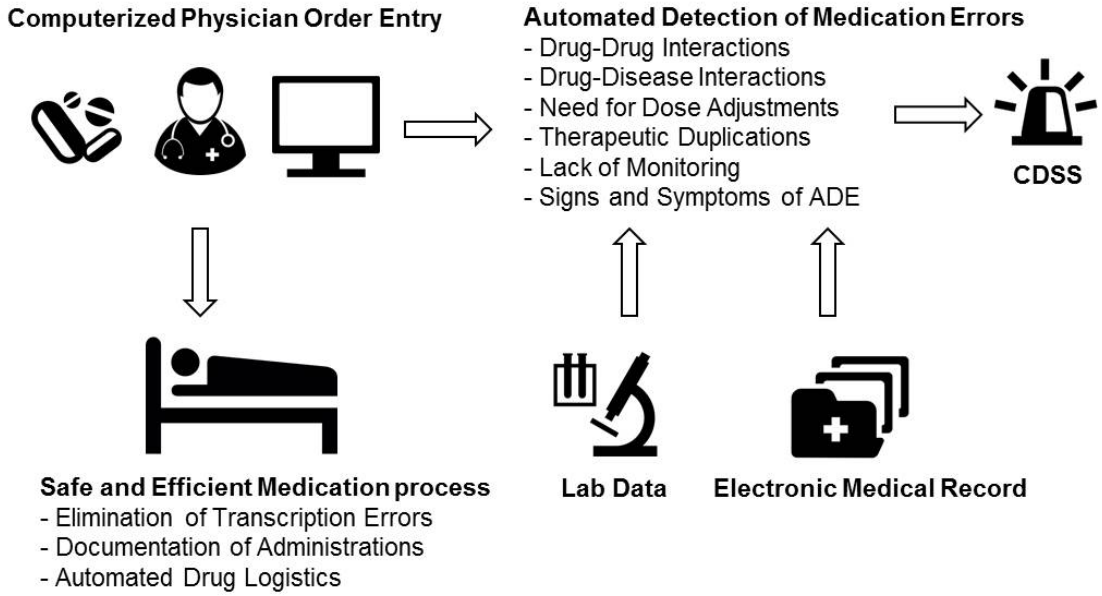


Figure 4: Potential Contribution of Computerized Physician Order Entry (CPOE) and Clinical Decision Support Systems (CDSS) to Increase Drug Safety. The overall comprehensive integrated information system managing all related data is designated Clinical Information System (CIS). Adapted from: Arzneimitteltherapie, Wirksamkeit, Sicherheit - Praktische Anwendung, page 31.

Some CDSS are available for free, can be used on mobile devices and use public knowledge databases. Depending on the hospital, CDSS may also be highly customized to local clinical practice and adapted to the used CPOE and CIS using specially developed interfaces. The knowledge displayed in CDSS and used for decision support algorithms may be based on textbooks, official national and international summary of product characteristics (SPC), peer-reviewed scientific publications or pharmacovigilance data. Comparisons of individual CDSS have shown considerable differences regarding the identification, categorization and concordance with clinical assessment of DDI.[27-29]

2.3.2. Alerts: Acceptance, Fatigue and Override Rates

Advice regarding the prevention of ME that were identified by a clinical pharmacologists or clinical pharmacists or can improve patient-related outcomes and reduce costs.[30-32] If such advice is provided face-to-face, e.g. during clinical ward rounds, it can reach rates of acceptance by clinicians of approximately 80 - 90 %, depending on the setting, threshold for- and nature of such advice.[33,34] Automated alerts for the prevention of ME also need to accurately identify clinically relevant ME and provide meaningful management-suggestions such as therapeutic alternatives, adequate dose reductions or practical recommendations regarding therapeutic drug monitoring.[26] However, despite intense and ongoing efforts to improve CDSS, alerts from fully automated systems are usually only accepted by clinicians in approximately 5-10 %.[35] Physicians who are repeatedly exposed to high numbers of alerts - which are consistently not leading to clinical problems - may develop a "pragmatic skepticism regarding the daily false alarms" issued by CDSS, especially for DDI (Briant et al. 2014).[36] They acknowledge that high alert override rates may lead to potentially valuable warnings being ignored,[37,38] but state that due to the excessively high number of alerts they receive, the warnings are perceived to be of low-value in general.[39,40] Although the sheer number of alerts is usually found to be associated with their poor acceptance by clinicians,[41] the concept of alert fatigue has recently been challenged - suggesting that there are other, more important factors that lead to alert fatigue, foremost the perceived lack of clinical relevance. Besides the involved drugs and type of DDI, factors associated with alert override include age of physicians and patients, unit of hospitalization, number of daily alerts and lengths of patients' stay. [36,42] Unfortunately, "current CDSS have been found to be least effective when they should protect the most vulnerable patients from the most dangerous medications, particularly when they are prescribed by the most inexperienced physicians" (Knight et al. 2015).[35]

Pharmacotherapy with DDI that trigger automated alerts has been studied extensively, and usually similar drugs appear in the 'top 20' that generate the most alerts.[43] However there is little evidence that alerts regarding these drugs are associated with a higher acceptance or clinical relevance.[35] Most commonly used CDSS for the prevention of DDI do not consider the drugs dose and are not (yet) using additional patient-specific information, which is likely a key factor in order to improve the current lack of their clinical relevance.[26,29] Alerts by CDSS are usually divided into categories of severity and include information on the background, mechanism, recommendation and consequence of potential ME.[44]

Recently published recommendations suggest that alerts for DDI should contain the following 7 information components: “drugs involved, seriousness, clinical consequences, mechanism of the interaction, contextual information / modifying factors, recommended actions and evidence” (Payne et al. 2015)[26]
Irrespective of the role of alert fatigue, inappropriate alert overriding for DDI and drug related allergies has been reported to be involved in ADE.[45,46] Numerous recommendations for improving alerts exist, and these suggest a categorization of alerts according to the severity of the expected outcome into non-interruptive alerts vs. high priority DDI that should not be allowed at all.[47-49] Furthermore it has been suggested that the alerts should be presented using “a consistent use of terminology, visual cues, minimal text, formatting, content, and reporting standards to facilitate usability” (Briant et al. 2014).[36]

2.4. Comprehensive Hospital Drug Safety Concept

2.4.1. Hospital Safety Culture

Improving hospital drug safety requires more than just a fully automated CDSS, it requires the implementation of a comprehensive concept. The following section provides a conceptual framework developed by Stefan Russmann that links previous research in this field with clinical practice, existing safety systems and complementary methods from pharmacovigilance and pharmacoepidemiology to be applied by local drug safety experts.[50]

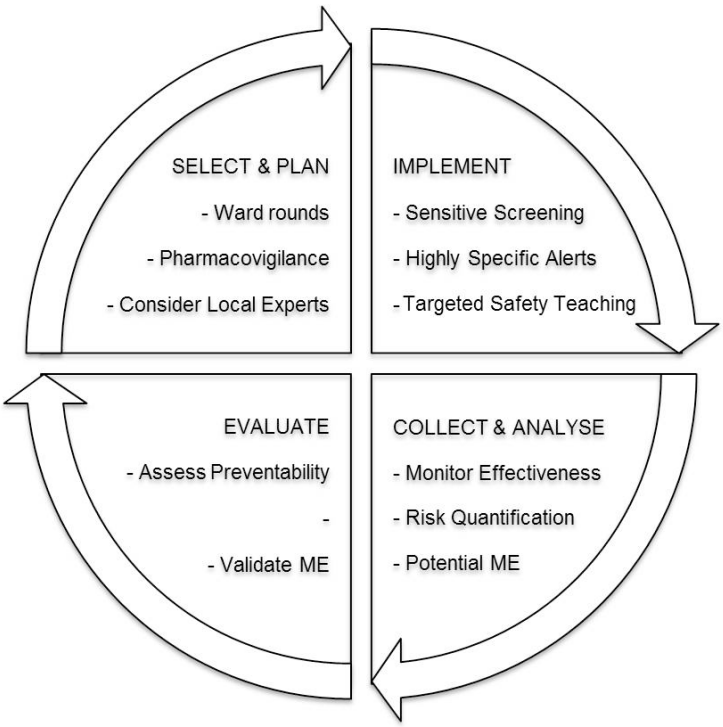


Figure 5: Broad Integrative Concept for Improved Hospital Drug Safety, closed quality loop concept adapted from: Russmann S, Praxis und Perspektiven der Arzneimittelsicherheit: Pharmakovigilanz, Pharmakoepidemiologie und elektronische Expertensysteme, Ärztewoche 2012 and described in SNF Project Nr. 143867.

2.4.2. Selection and Planning

Performing regular safety ward rounds contributes to the promotion of a local hospital safety culture. Individually reviewing the pharmacotherapy of currently hospitalized patients for ME and using their electronic medical records to detect ADE may not be efficient for reducing the absolute number of ME. But the highly specific recommendations contribute to individual patient's safety and a generally increased awareness of the prescribers for drug safety issues. Although not formally evaluated, it was observed that regular participation during ward rounds at the Department of Neurology resulted in an increased reporting rate of ADE and persistent implementation of orally communicated recommendations, such as the age-dependent use of zolpidem or the use of pantoprazole instead of omeprazole in patients using clopidogrel.

Face-to-face recommendations to the prescribers, local clinical expertise and regular safety ward rounds make major contributions to the detection of ME. Seeing patients exposed to potential ME in their comprehensive clinical context and subsequent feedback from the prescribers is invaluable for the development of highly specific alert algorithms. Detecting and reporting ADE during ward rounds contributes to proactive pharmacovigilance and may aid to the further detection of clinically relevant ME. Finally, participation of local drug safety experts in ward rounds also allows to complement the detection of "near misses" that are not reported to critical incident reporting systems (CIRS), i.e. an anonymized system where hospital personnel can voluntarily report potential or actual safety issues.

2.4.1. Implementation

CIS that feature integrated, currently available CDSS may allow a highly sensitive on-demand screening for potential ME related to DDI in individual patients. Typically, these systems rarely use additional patient-specific information and are not setup to issue automated alerts for all potential ME due to the above-described issue of overalerting. A recent system analysis at the University Hospital of Zurich revealed that the integrated on-demand CDSS for DDI is rather used almost exclusively as a screening tool by local drug safety experts such as clinical pharmacologists and pharmacists whereas physicians treating patients and prescribing their pharmacotherapy in first-line rarely use it.[34]

Complementary to such highly sensitive but insufficiently specific and efficacious screening tools, additional highly specific alerts have recently been developed and

implemented. Besides the automated alerts regarding acetaminophen and metformin subsequently presented in this thesis, warnings regarding the prevention of venous thromboembolism[51,52], drug-induced hyperkalemia[53] and methotrexate overdosing[54] have recently been successfully implemented. Besides specifically developed automated alerts personal teaching of prescribing physicinas regarding current safety issues, e.g. drug-induced QT-prolongation, remains an important local contribution for the improvement of drug safety.

2.4.2. Creation of a Local Pharmacoepidemiological Database

A major part of the presented thesis is the creation of a local pharmacoepidemiological database based on an existing electronic CIS (see also chapter 2.1). It used the following data extracted on patient-level:

- ATC-code of relevant drugs to identify the used drugs
- Name of applied drug as entered into the electronic medical records
- Date and time of drug administrations
- Applied drug dose
- Route of administration such as oral, intravenous, etc.
- Potassium and creatinine levels (lab data)
- Age of patient in years at time of administration of drug (in 2011 or 2012)

Incomplete raw data after an automated extraction, such as missing ATC-codes, may be complemented manually for some of the parameters, especially if free-text entries were allowed upon prescribing drugs in the CPOE. Implausible data, such as non-physiological potassium values due to haemolysis, also need to be corrected or marked as missing if applicable. The database then must be thoroughly checked for quality, plausibility and validity. Two principal methods can be applied in order to characterize prescription patterns and to detect potential ME: Either fully automated mass-analyses can be performed by using commercially available CDSS. This requires a high quality of the extracted data and a corresponding interface for the CDSS to process the data. Alternatively, individual algorithms for the detection of potential medication errors can be developed, programmed and then applied to the data. Such an approach allows a more specific assessment of certain ME.
Data extracted from the CIS can also be used to monitor effectiveness of preventive strategies, e.g. by assessing the prevalence of potential ME before and after implementation of a newly implemented alert.

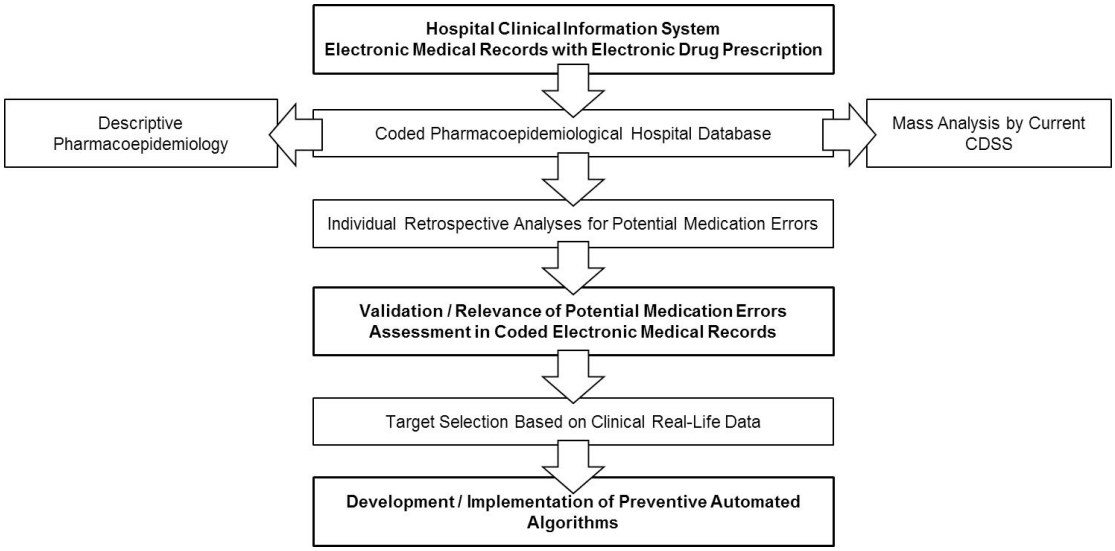


Figure 6: Interventional Pharmacoepidemiology, concept adapted from: Cartwright on Russmann in International Innovation 2014.[55] Processes involved for developing and implementing new preventive algorithms based on the raw data extraction of documented drug administrations in the hospitals CIS.

2.4.3. Evaluation

In order to validate potential ME regarding their clinical relevance, retrospective review of selected original electronic medical records in the CIS is necessary. This allows the detection of expected ADE known to be associated with the respective ME. By specifically searching for an ADE during an appropriate time window following the potential medication error, clinical relevance can be established. If for example, an overdose of paracetamol, a drug known for its dose-dependent liver-toxicity, is detected, a specific search for signs (i.e. increase in liver enzymes) and symptoms (e.g. nausea, vomiting, jaundice) of liver disease in the days following the overdose can be performed. Additionally, by reviewing the electronic medical record of the exposed patient, certain risk factors for paracetamol toxicity that are not available in the pharmacoepidemiological database, such as alcoholism or anorexia, can be detected. Furthermore, alternative causes for liver disease such as viral hepatitis or exposure to other liver-toxins must be assessed and excluded. Subsequently a formal causality assessment according to WHO / CIOMS can be performed for a semi-quantitative assessment of the relation of ME and ADE.

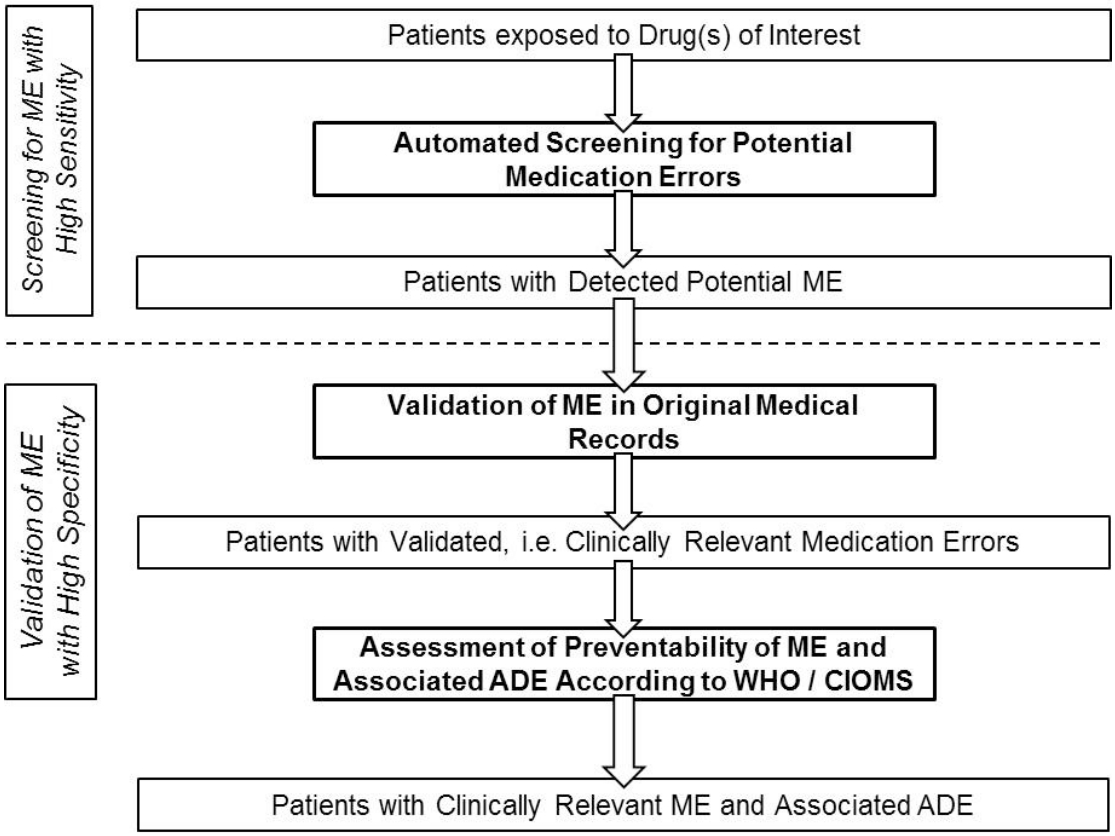


Figure 7: Detail of the Setup for Validating Potential ME as Detected in a Hospital Pharmacoepidemiological Database: Assessment of clinical relevance, associated ADE and preventability by compilation of additional parameters as documented in the patients' electronic medical records.

Because the structured data that was extracted for the compilation of the pharmacoepidemiological database does not encompass all information that is available and necessary for the validation of potential ME, the following additional parameters can be of special interest and may need to be compiled manually or have to be extracted additionally in order to efficiently validate the clinical relevance of potential ME:

- Indication of studied drugs
- Liver function parameters
- Plasma protein levels
- Heart- and muscle parameters
- Glucose and lipid-metabolism parameters
- Endocrine functions
- Drug levels from therapeutic drug monitoring, substance- and alcohol levels

- Blood gas analyses
- Infectious parameters
- Immune system parameters
- Blood pressure and heart rate
- ECG readouts
- BMI / nutritional status

The validation of potential ME therefore requires access to the patients' complete electronic medical records including entry- and discharge reports, anesthesia- and surgical reports, counsels, nurses' and physicians' ward round reports and any other notes documenting suspected or confirmed ADE. Only such an encompassing analysis allows consideration of the clinical context of potential ME and provides the information to understand the physicians benefit-risk assessment upon prescription.

2.5. Ethical Considerations and Data Protection

The studies presented in this thesis were primarily of non-interventional, observational character using only already existing data. Nevertheless, any such study is subject to the new Federal Act on Research involving Human Beings, also known as Human Research Act, HRA) as effective since January 2014.[56] Therefore the research presented in this study needed to be re-assessed by the ethics committee in 2014 to which the following statements were presented:

The primary goal of the presented studies was the identification and subsequent reduction of risks associated with pharmacotherapy, and they are expected to improve patient safety. Since all analyses were performed with already collected data that was further used for research, the retrospective analyses for potential medication errors posed no immediate risk for patients. A potential risk would have been an unwanted identification of project participants from published results. However, only anonymous results were published. Unwanted identification of patients was also prevented by the coding of the dataset, e.g. study-files did not contain any non-encoded information such as patient's names or initials. No patient-related data was distributed by Email. Any data displayed in any presentations, scientific conventions or in scientific journals was anonymous. For the identification of patients in the CIS the case number issued by the University Hospital Zurich served as a unique patient identifier.

Data generation, transmission, storage and all analysis of health related personal data for the presented study strictly followed current Swiss legal requirements for data protection and were performed according to the Ordinance HRO Art. 5. All investigators were fully aware that the presented studies involved potentially sensitive and strictly confidential personal data. All investigators were healthcare professionals (pharmacists and clinical pharmacologists) who are generally bound to medical confidentiality and additionally signed an obligation featuring the following measures to guarantee data protection:

- Access to computers must be password protected, see criteria for these passwords below
- Access to all study files must be password protected, see criteria for these passwords below
- All passwords will be changed every 6 months and must contain at least 12 digits and must contain at least one special character and must at least contain one capitalized letter and must contain at least one non-capitalized letter and must contain at least one number.
- Passwords must never be passed-on, or stored, or saved in any way.
- Whenever the workplace is left, the computer(s) must be locked.
- If accessing patient's original electronic medical records, only potentially error-specific parameters and reports will be reviewed.
- All study related data must exclusively be handled and stored on encrypted data mediums. The BitLocker technology of Microsoft and the FileVault technology of MacOS were used to guarantee a high level of data-protection.

Every access to every document within the patients' electronic medical records was automatically logged by the CIS of the University Hospital of Zurich to prevent abuse. No coding in the formal sense of HRO Art. 26 and 27 was applicable. However, patients' numbers are used to combine parameters from drug prescriptions, documented drug administrations, lab data and other data (such as ECG, blood pressure, co-morbidities etc.) for all analyses and therefore represent a code to identify a patient. In order to identify a patient through the patient's number one needs access to the clinical information system of the University Hospital of Zurich. However, access to the clinical information system is only granted under the condition of medical confidentiality. The patients' numbers therefore serve as encoding to prevent unauthorized patient identification: Without access to the clinical

information system under the condition of medical confidentiality it is not possible to determine the patients' identities with the patient number.

The validation of potential medication errors in selected electronic medical records required review of non-anonymized existing data. Such additional non-routine access to the already existing data imposes no direct burden or risk to the patient. The investigators act under their routine mandate of pro-active quality-management of hospital pharmacotherapy and patient safety. There was no special risk or burden for vulnerable patients. Indeed, in some situations such patients may have been especially vulnerable for certain medication errors and were therefore expected to benefit at least as much or even more than other patients.

In summary the performed studies presented no risk for the patients. To the contrary, the primary aim of the studies was the systematic identification of risks and subsequent improvement of patient safety. Furthermore the performed studies are beneficial for the hospital and its prescribers due to a pro-active quality management that aimed for a reduction of ME and associated ADE, reduces avoidable costs, and prevents potentially considerable reputational damage.

The cantonal ethics committee, the hospital’s medical director and the hospital’s center for clinical research had approved the data extraction, the setup and analysis of the anonymized pharmacoepidemiological database, and the access to original medical records for research purposes.

3. Results

3.1. Creation of a Pharmacoepidemiological Database: Highly Efficient Pharmacoepidemiological Analysis of Hospital Drug Prescriptions with Target Identification for the Prevention of Medication Errors

3.1.1. Authors

David Niedrig, Caroline Schmidt, Stefan Russmann

3.1.2. Remarks

Significance for thesis & notable features

The creation of a local pharmacoepidemiological database was the first milestone of this thesis and literally represents the (data)base for all subsequent studies regarding ME in hospitalized patients hereafter presented. It is designed for analyses by highly efficient algorithms that can detect a multitude of potential ME. Developing, programming and validating these algorithms provided crucial information to prioritize targets for further in-depth analyses of potential ME.

The raw data is derived from multiple components of the CIS of the University Hospital Zurich, i.e. KISIM by Cystec AG. Whereas the raw data extracted from the CIS comes from an underlying relational database where the data is arranged and stored in a large number of different files that can be linked with a unique patient identifier, the master file of the pharmacoepidemiological database was created as a single file using STATA (STATA Corporation, College Station, TX, USA). Of special interest not only drug prescriptions by the physician, but also their actual administration (or non-administrations) confirmed by the drug-administering staff are documented in the underlying raw data. Only confirmed drug administrations were used for all further analyses. At the time of extraction no comparable database was available for such a highly efficient, systematic exploration of potential ME.

Contributions of the author of this thesis

David Niedrig compiled, structured and formatted the database, developed the algorithms and performed database- and algorithm validation.

Publication

This study was presented as an abstract and poster at the Pharmacology & Toxicology Poster Day 2013 in Zurich.

3.1.3. Background

Electronic medical records with electronic drug prescription provide new opportunities for pharmacoepidemiological analyses in health care systems. Very large automated pharmacoepidemiological databases have recently been established in several countries and become a leading source of information for research and public health decision-making. In contrast, the potential of “small-scale hospital pharmacoepidemiology” for local improvements of pharmacotherapy, pharmacoeconomics and particularly drug safety is not sufficiently used.

3.1.4. Objectives

Therefore, we developed new concepts and solutions for data management, analyses and proactive quality and safety management of hospital pharmacotherapy.

3.1.5. Methods

We obtained comprehensive anonymous patient level drug prescription data plus selected laboratory results of a tertiary care hospital for the calendar years 2011 and 2012. Raw data comprising >7 million lines of text were reformatted, additional codes included and variables generated, and the data was optimized for fast and efficient analyses. Data management and analyses were executed on a high performance computer system and software that can simultaneously run on four processor cores. For our final analyses we included only those prescriptions that were flagged as actually administered to patients.

3.1.6. Results

We successfully completed the development, quality control and validation of a pharmacoepidemiological hospital prescription database. Subsequently, we developed analytical protocols for the ultra-fast identification of potential medication errors that allowed us to retrospectively find and validate a considerable number of specific real-life contraindicated and/or critical prescriptions in individual patients. Sensitivity and specificity regarding clinical relevance was enhanced by the use of additional patient-level laboratory data and repeated validation procedures.

3.1.7. Conclusions

The presented methods and results provide the basis for the development and implementation of automated alerts that are sufficiently sensitive and specific for use in clinical practice. These are expected to achieve effective and efficient improvements of pharmacotherapy leading to a relevant reduction of medication errors and associated adverse reactions and costs.

3.2. Retrospective Mass-Analysis of Hospital Prescription Data for Medication Errors and Subsequent Development of Highly Specific Alert Algorithms with ID PHARMA CHECK®

3.2.1. Authors

David F. Niedrig, Andre Sander, Daniel Diekmann, Stefan Russmann

3.2.2. Remarks

Significance for thesis & notable features

This study complements the initial individual analyses of individually selected potential ME by using a commercially available CDSS. Unlike many other currently available CDSS, ID PHARMA CHECK® considered the dose of the drugs, available lab data and codes for diagnoses, allowing an assessment of potential drug-disease related ME and many other fully automated analyses. As expected, such a highly sensitive screening generated an excessively high number of alerts that were summarized in 166 individual lists. Focusing on the list with ME with a clear potential for severe ADE, i.e. the list of absolutely contraindicated DDI, the manufacturer of the CDSS was provided with suggestion regarding the improvement of the specificity of these alerts.

Contributions of the author of this thesis

David Niedrig contributed to the assessment of the clinical relevance of detected potential ME and the subsequent development of suggestions to improve the alerts for contraindicated DDI.

Publication

This Study was presented as a poster and abstract in 2015 at the International Conference of Pharmacoepidemiology (ICPE) in Boston, MA, USA. It was also presented as a poster, abstract and oral presentation at the Congress of the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) 2015 in Zurich where it won the award for the congress' best oral presentation.
It is published as a congress abstract in: Pharmacoepidemiology and Drug Safety 2015; 24: 65-66.

3.2.3. Background

Clinical decision support software (CDSS) identifies potential medication errors in individual patients, typically with a focus on high sensitivity but low specificity regarding clinical relevance. Our concept of Interventional Pharmacoepidemiology applies real-life data to retrospective analyses of medication errors in order to identify targets for highly specific alerts that can effectively prevent the most relevant medication errors.

3.2.4. Objectives

We aimed to identify and quantify medication errors that actually occur in clinical practice and use the results for programming CDSS alert algorithms with high specificity regarding clinical relevance.

3.2.5. Methods

We applied real-life data from a clinical information system of a tertiary care hospital covering one calendar year and approximately 250’000 patient-days and 3.5 million individually documented drug administrations along with laboratory results and medical diagnoses to retrospective mass-analyses using the ID PHARMA CHECK® database. Identified potential medication errors were quantified and used for the development of refined alert algorithms.

3.2.6. Results

ID PHARMA CHECK® identified several ten thousand potential drug interactions, contraindications and dosing errors, and assigned them to formal severity categories. There were 3’460 cases of 64 distinct formally contraindicated drug interactions. Among those we evaluated 48 interactions as clinically relevant and suitable for display of highly specific alerts within clinical information systems; 32 alert algorithms require retrieval and implementation of current patientspecific information such as laboratory results in order to reach high specificity. The resulting algorithms were subsequently programmed for routine use with ID PHARMA CHECK®.

3.2.7. Conclusions

Application of CDSS to large prescription datasets can retrospectively identify medication errors and therefore play an important role for proactive quality management of pharmacotherapy in hospitals. Vice versa systematic mass analyses of real-life data can support CDSS development with a focus on clinical relevance and efficacy.

3.3. Second-generation antipsychotics in a tertiary care hospital: prescribing patterns, metabolic profiles, and drug interactions

3.3.1. Authors

David F. Niedrig, Carmen Gött, Anja Fischer, Sabrina T. Müller, Waldemar Greil, Guido Bucklar, Stefan Russmann

3.3.2. Remarks

Significance for thesis & notable features

This study was the first in-depth analysis of potential ME related to a specific group of drugs within the local hospital pharmacoepidemiological database and the CIS of the University Hospital Zurich. Besides analyzing well known and potentially severe ME related to DDI it also takes advantage of ethically approved access to original electronic medical records. Equally important drug safety aspects of pharmacotherapy with second-generation antipsychotic drugs, i.e. their potential to induce metabolic complications, was explored and a significant potential for improvements regarding their monitoring and management was detected. Obtaining reliable information on the indication of drugs is challenging in pharmacoepidemiology. This study features the categorized indications of second-generation antipsychotics as documented in the patients' original medical records and revealed a high proportion of off-label use for these drugs. Additionally, laboratory data on multiple metabolic parameters and leukocytes was systematically evaluated in order to assess monitoring for ADE.

Contributions of the author of this thesis

David Niedrig contributed to the study design, algorithm development and programming, data compilation and interpretation, and wrote the first version of the manuscript.

Publication

This Study has been published as original research in: International Clinical Psychopharmacology: January 2016; 31(1): 42-50.

3.3.3. Background

Second-generation antipsychotics (SGA) are primarily indicated for the treatment of schizophrenic disorders, and some SGA such as quetiapine, risperidone, aripiprazole and lurasidone also have labeled indications for other psychiatric disorders including bipolar diseases. A pronounced rise in the use of antipsychotics has been observed over the past 20 years, which is mostly attributable to the increased prescription of SGA since their introduction in the mid 90's.[57,58] Off-label use has also been reported to be very common for SGA in clinical practice, e.g. for the treatment of dementia and symptoms of anxiety, sleep and neurotic disorders.[59,60]

SGA are not generally more effective than first-generation antipsychotics (FGA),[61] but they have a distinct profile of adverse effects. Fewer extrapyramidal adverse effects are traded for more metabolic adverse effects including weight gain, hyperglycemia and dyslipidemia.[62,63] The risk of such metabolic abnormalities appears to vary for different SGA, and to lower this risk has been an important goal in the development of more recently approved substances such as aripiprazole, ziprasidone and lurasidone.[64,65] Nevertheless, current drug labels as well as international guidelines recommend that the metabolic profile should be monitored before and during treatment with SGA, particularly in patients with preexisting metabolic disorders and other cardiovascular risk factors.[66] Therefore, studies on the frequency of metabolic disorders, their management, and the actual implementation of labeled recommendations in SGA users in routine clinical practice are an important contribution for the post-marketing evaluation of real-life risks and benefits of SGA.[57,66]

Furthermore, SGA can prolong the QTc interval with an associated increased risk of ventricular arrhythmia and sudden cardiac death.[63,67] The risk for cardiac and other adverse drug reactions may be enhanced by clinically relevant drug interactions. Pharmacokinetic interactions may occur with inducers or inhibitors of the CYP450 enzyme system and may alter the plasma concentrations of SGA such as the CYP3A4 substrates clozapine and quetiapine. Pharmacodynamic interactions may also be problematic, e.g. when several QT-prolonging drugs are combined. Consequently a considerable number of drug combinations with SGA are labeled as formally contraindicated, and other potentially interacting combinations have labeled warnings requiring that the risk-benefit ratio must be carefully assessed, and that close monitoring for adverse events must be performed. However, there is limited real-life data on the actual prevalence and clinical relevance of potentially interacting co-medication with SGA.

3.3.4. Objectives

The trend towards increased use of SGA may also be observed in tertiary care hospitals where patient characteristics, indications and usage patterns are different compared to psychiatric hospitals or outpatient settings. The current study therefore had three main aims that we wanted to evaluate in the real-life setting of a tertiary care hospital. First to explore prescribing patterns of SGA, second to analyze how metabolic complications of patients receiving SGA are monitored and managed, and third to analyze the prevalence, monitoring and clinical relevance of potential drug interactions with SGA.

3.3.5. Methods

We conducted a retrospective observational study that analyzed SGA use and related population characteristics, metabolic profiles, concomitant pharmacotherapy and adverse events in a tertiary care hospital. The cantonal ethics committee, the hospital's medical director and the hospital's center for clinical research had approved the data extraction, the setup and analysis of the anonymized pharmacoepidemiological database and the access to original medical records for our research studies.

Data Source

For the current study we used comprehensive data for the time period from 1 January 2011 to 31 December 2012 from our anonymized pharmacoepidemiological database containing information on demographics, laboratory results and electronic drug prescriptions for hospitalized patients of a tertiary care hospital. The hospital provides medical care to a population of about 1.5 million people and has approximately 1000 beds and 40 clinical specialty divisions. The database builds on information extracted from the hospital's electronic clinical information system featuring electronic drug prescription (computerized physician order entry, CPOE). The system records not only prescriptions but also a confirmation for each drug's actual administration (and its time) to the patient. Our analyses included all prescriptions with documented administration from all hospitalized patients during the study period, except patients staying at intensive care units, where CPOE has not yet been introduced. We performed extensive reformatting, quality controls and matching of ATC codes to ensure identification of all administered drugs and their doses. In addition, we also compiled information on indication for SGA use, metabolic

parameters, blood counts and ECG QTc-interval measurements for the population of the current study.

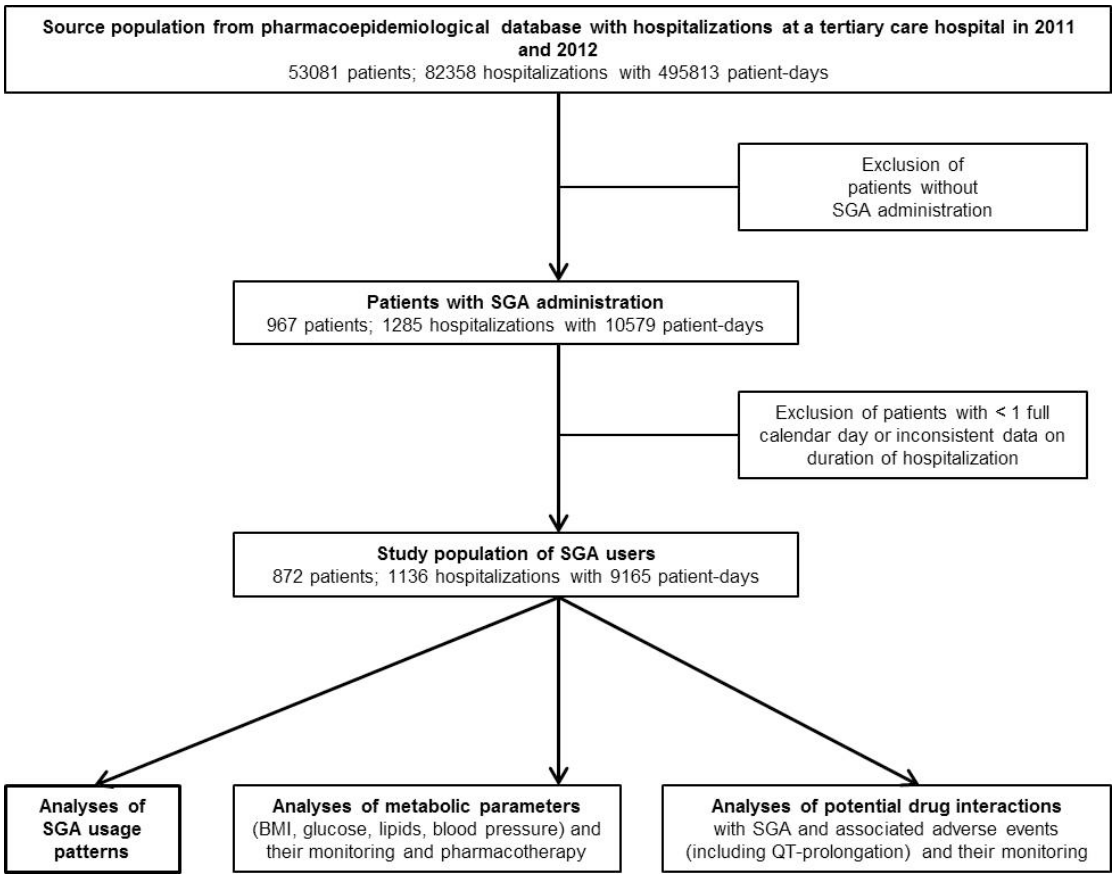
Study population and design

Selection of the study population and the overall study design are presented in **Figure 8**. All patients with at least one full calendar day of hospitalization and a documented administration of SGA were included into the study. The admission and the discharge day of each hospitalization were excluded from our analyses because drug administrations and events are not comprehensively recorded in the available data for those days. We included all SGA from our dataset that were defined as such by the US Federal Drug Administration and the German Psychiatrist's Association,[68,69] i.e. amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone. Within the resulting study population we analyzed the following outcomes: 1. SGA usage patterns; 2. metabolic parameters and their monitoring; 3. potential drug-drug interactions including associated adverse events and their monitoring.

SGA usage patterns

SGA use was descriptively analyzed regarding patient characteristics, primary diagnoses, indications and prescription frequencies. Indications for SGA use were determined according to all related information found in the electronic medical records and classified to one of the following 7 categories: 1. endogenous psychotic disorders (schizophrenia, schizoaffective disorders, other psychotic non-organic disorders); 2. exogenous psychotic disorders (substance induced behavior disorder or delirium, delirium in acute organic psychosis, dementia in chronic organic psychosis); 3. affective disorders (bipolar disorder with depressive or manic episode, depression); 4. personality disorder (borderline, emotional instability, other); 5. anxiety disorder and state of anxiety or excitation; 6. sleeping and eating disorders; 7. other indications (hallucination, agitation, somatogenic psychic disorder).

Figure 8: Study design and selection of the study population



Metabolic parameters and their monitoring

Metabolic abnormalities were defined according to a published joint scientific statement of six international organizations and assessed for each hospitalization. Mean blood pressure was calculated from the first documented measurement on each patient day with SGA exposure for each hospitalization.[70] Body mass index (BMI) was calculated from the first recorded measurement of height and weight during hospitalization or, if not available, derived from other information on nutritional status in the medical records. For metabolic laboratory values (blood glucose, HbA1c, and blood lipids) all measured values during hospitalization were recorded. We identified treatment with antidiabetic, antihypertensive and lipid-modifying drugs, and we also recorded treatment with glucocorticoids because these may increase blood glucose and therefore act as confounders.

Potential drug interactions and associated adverse events

We identified potential drug-drug interactions of SGA with all contraindicated drugs that were administered on the same calendar day. For that purpose we first established a list of formally contraindicated drugs according to the manufacturers' national drug labels for each SGA (www.swissmedicinfo.ch). For labeled contraindications that referred to specific drug characteristics (e.g. drugs known to cause QTc prolongation, agranulocytosis or drug metabolizing CYP450 enzyme inhibition) we established lists of drugs fulfilling those criteria. These were based on comprehensive available scientific information sources including specialized drug interaction software and websites.[71-75] For drug combinations with SGA that were not formally contraindicated but require careful monitoring of the QTc-interval according to the manufacturers' national drug labels, we established additional lists with the drugs' Anatomical Therapeutic Chemical Classification System (ATC) codes. For all potentially interacting drugs that prolong QTc interval or inhibit CYP450 enzymes, we only included drugs that exhibit a strong or moderate effect according to at least one reference. We only analyzed hospitalizations where at least one strong CYP450 inhibitor or at least two moderate CYP450 inhibitors were co-administered at the same patient day. For every hospitalization for which we identified potential interactions with SGA, we validated whether any adverse events known to be associated with those interactions had actually occurred, and whether active monitoring for such events had been performed. We reviewed the original medical records for any events and clinical diagnoses that might represent an adverse drug reaction caused by the respective drug interactions. We checked whether ECG was monitored on days on which SGA were co-administered with contraindicated or

potentially critically interacting drugs. Monitoring for QTc-prolongations was evaluated by reviewing all ECGs of all hospitalizations with QTc-prolonging drug combinations in the medical records. A QTc-interval >450 ms in men and >460 ms in women is associated with increased cardiovascular mortality and defined the upper limit of normal by the American Heart Association, and this was accordingly categorized as "abnormal QTc" for the present study. A QTc-interval >500 ms significantly increases the risk of Torsades de Pointes tachycardia and sudden cardiac death and was defined as "long QTc" in our study.[73,76]

For contraindicated drug combinations with an increased risk of agranulocytosis that had been co-administered for at least three consecutive days, we reviewed results of all available blood counts. Neutropenia was defined as a neutrophil blood count <1.4 G/l, and agranulocytosis as a count <0.5 G/l.

If an associated adverse event was documented, three investigators with special expertise in pharmacovigilance and formal causality assessment (SR, DN and CG) assessed the causal relationship of the adverse event with the interacting drug combination using internationally standardized WHO/CIOMS causality assessment criteria.[2]

Data analysis

Data analysis is descriptive with presentation of results in tables as appropriate. Frequencies were calculated regarding individual patients, hospitalizations and patient days. Data management and analyses were done using STATA Version 13.1 (STATA Corporation, College Station, TX, USA).

3.3.6. Results

The source population consisted of 53081 individual hospitalized patients contributing 82358 hospitalizations and 495813 patient-days. After exclusion of patients without SGA use and less than at least one full calendar-day of hospitalization the resulting study population included 872 patients with 1136 hospitalizations and 9165 patient-days. In total, we analyzed the circumstances of 14214 single SGA administrations (Figure 8).

SGA usage patterns

Characteristics of the study population are presented in **Table 1**. Females accounted for SGA use in 50.9% of the hospitalizations and 60.1% of the patient-days. Mean and median duration of hospitalization for all patients on SGA was 14 and 7 days,

respectively. Quetiapine was the most frequently used SGA in the studied population (46.7% of all patient-days with SGA exposure), followed by olanzapine (27.9%) and risperidone (13.7%). The three most frequently co-administered drug groups with SGA were analgesics (ATC class N02, 8210 patient days, 10.0% of all co-administered drugs), antithrombotic agents (ATC class B01, 7485 patient days, 9.2%) and psychoanaleptics (ATC class N06, 6027 patient days, 7.1%). The small unit of psychiatry and psychotherapy (accounting for only 2.2% of all patient-days in the source population) expectedly had the highest prevalence of SGA use (on 23.8% of the patient-days in the unit) and accounted for 19.3% of all patient-days with SGA exposure in the hospital. The remaining 80.6% of SGA-use occurred in non-psychiatric units. In the neurology unit SGA were used on 6.5% of the patient-days, representing 14.5% of all SGA use at the hospital. Besides the psychiatry and neurology units, we found the highest prevalence of SGA exposure in the units of plastic surgery and infectious diseases (on 4.2% and 4.0%, respectively, of all patient days in these units). Due to their large absolute number of hospitalizations, trauma surgery and internal medicine were also major contributors to SGA use in the studied population (9.8% and 9.5%, respectively, of all patient-days with SGA exposure in the hospital). Indications for SGA prescriptions were identifiable in 899 hospitalizations and are also presented in **Table 1**. Affective disorders (31.9%), endogenous psychotic disorders (24.9%) and exogenous psychotic disorders (19.6%) were the three most frequent documented indications for SGA. Most common primary diagnoses of patients receiving SGA during hospitalization according to their documented ICD-10 codes were cerebrovascular disorders (ICD codes I60-I69, 4.2%), behavioral disorders with somatic disorders and factors (ICD codes F50-F59, 3.9%) and other forms of heart disease (ICD codes I30-I52, 3.9%). During most hospitalizations only one SGA was administered per day, but in 5.7% of the analyzed hospitalizations two SGA were administered simultaneously on at least one patient-day, and in 0.2% three SGA.

TABLE 1: Characteristics of the study population of second-generation antipsychotics (SGA) users in a tertiary care hospital

Characteristics	Hospitalizations n (%)	Patient-days n (%)
All analyzed SGA users	**1136 (100)**	**9165 (100)**
Sex		
Female	578 (50.9)	5506 (60.1)
Male	558 (49.1)	3659 (39.9)
Age (years)		
<18	8 (0.7)	131 (1.4)
18-44	280 (24.6)	3119 (34.0)
45-64	430 (37.9)	2787 (30.4)
65-84	357 (31.4)	2766 (30.2)
≥85	61 (5.4)	362 (3.9)
Use of different SGA[1]		
Quetiapine	599 (52.7)	4276 (46.7)
Olanzapine	234 (20.6)	2543 (27.9)
Risperidone	170 (15.0)	1214 (13.7)
Clozapine	115 (10.1)	866 (9.4)
Aripiprazol	51 (4.5)	379 (4.1)
Amisulpride	22 (1.9)	102 (1.1)
Paliperidone	13 (1.1)	49 (0.6)
Ziprasidone	1 (0.1)	11 (0.1)
Units with highest use of SGA[2,3]		
Neurology	167 (14.7)	1325 (14.5)
Trauma surgery	134 (11.8)	900 (9.8)
Internal medicine	92 (8.1)	873 (9.5)
Neurochirurgy	66 (5.8)	455 (5.0)
Plastic surgery	66 (5.8)	457 (5.0)
Psychiatry-psychotherapy	37 (3.3)	1772 (19.3)
Documented indications for SGA use[4]		
Affective disorders	287 (31.9)	1897 (24.3)
Endogenous psychotic disorders	224 (24.9)	1439 (18.5)
Exogenous psychotic disorders	176 (19.6)	1278 (16.4)
Sleeping disorders and eating disorders	84 (9.3)	2110 (27.1)
Anxiety disorders	57 (6.3)	593 (7.6)
Other	48 (5.3)	361 (4.6)
Personality disorders	23 (2.6)	115 (1.5)
No indication documented[5]	237 (20.9)	1372 (15)

Legend for Table 1

[1] *Total of hospitalizations / patient-days exceeds number of analyzed hospitalizations / patient-days due to use of multiple SGA on some patient-days. Total of % therefore exceeds 100.*

[2,3] *% of hospitalizations: hospitalizations of all analyzed cases with use of SGA (1136 hospitalizations)*
% of patient-days: prevalence of patient-days on these wards with use of any SGA in 2011 and 2012

[4] *% of hospitalizations where indication was available (899 hospitalizations)*

[5] *% of hospitalizations with no indication of all hospitalizations (1136) / % of patient-days with no indication of all patient-days (9165)*

Metabolic parameters, their monitoring and treatment

The monitoring of metabolic parameters in SGA users as well as the prevalence of metabolic disorders among those where monitoring was performed are presented in **Table 2**. Blood glucose and lipid profiles had not been determined in 24.3% (n=276) and 75.4% (n=856) of SGA users, respectively. In 58.3% of the cases in which any lab data on any metabolic status was available we found at least one metabolic abnormality. Furthermore, SGA users with prevalent metabolic disorders had no pharmacotherapy for those conditions in 63.4% of the hospitalizations with hyperglycemia, as well as in 70.8% and 37.1% with dyslipidemia and hypertension, respectively. Among all patients on SGA, 244 (28.0%) met the diagnostic criteria for metabolic syndrome as defined by a consensus group.[70] There were no apparent major differences in the prevalences of metabolic abnormalities between users of different SGA.

TABLE 2: Prevalence of metabolic disorders and of their monitoring and pharmacotherapy

	Absolute and relative frequencies
Total number of hospitalizations with SGA use	1136 (100%)
Obesity	
No weight, height or nutritional status documented	256 (22.6% of total)
BMI based on weight, height or additional data	880 (77.4% of total)
BMI ≥25 kg/m²	459 (52.1% of those with available BMI)
BMI ≥30 kg/m² (=“obesity”)	203 (23.1% of those with available BMI)
Glycemic disorder	
Blood glucose not measured	276 (24.3% of total)
Blood glucose values available	860 (75.7% of total)
Glycemic disorder[1]	194 (22.6% of those with glucose values)
Pharmacotherapy for diabetes	71 (36.6% of those with glycemic disorder)
Glucocorticoids co-administered	36 (18.6% of those with glycemic disorder)
Lipid disorder	
Blood lipids not measured	856 (75.4% of total)
Blood lipid values available	280 (24.6% of total)
Lipid disorder[2]	171 (61.1% of those with lipid values)
Pharmacotherapy for lipid disorder	50 (29.2% of those with lipid disorder)
Hypertension	
Blood pressure not measured	26 (2.3% of total)
Blood pressure values available	1110 (97.7% of total)
Hypertension[3]	410 (36.9% of those with blood pressure values)
Pharmacotherapy for hypertension	258 (62.9% of those with hypertension)

Legend for Table 2
Criteria for metabolic disorders were defined according to published consensus guidelines[77]
[1] Fasting glucose ≥5.6 mmol or spontaneous glucose ≥11.1 mmol/l or HbA1c > 5.9% (women) or >5.7% (men)
[2] Total cholesterol ≥5 mmol/l and/or HDL cholesterol ≤1mmol/l and/or triglycerides ≥1.7mmol/l
[3] Systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmH

Potential drug interactions and associated adverse events

Prevalence of combined use of SGA with drugs that are formally contraindicated, as well as with drugs that are not formally contraindicated but have a labeled high risk of QTc-prolongation in combination with SGA, are presented in **Table 3.**

Co-administration of formally contraindicated drugs with SGA was present on 614 patient-days emerging from 112 hospitalizations. Among those we identified 3 cases with clinically relevant adverse events that were related to the respective co-administrations with a “probable” causal relationship according to WHO/CIOMS causality criteria: one case with neutropenia and two with abnormal QTc. However, in 51 of the 112 hospitalizations, there was no monitoring of blood count or QTc interval, so the presence of related adverse events cannot be excluded for those patients. Co-administrations of QT-prolonging combinations that were not formally contraindicated but potentially dangerous were identified in 176 hospitalizations. Among those, ECG-monitoring for adverse events was performed in only 18 patients (10.2%), and among those we identified 2 cases with abnormal QTc and a “probable” causal relationship with the critical combination.

TABLE 3: Drug interactions with SGA including their monitoring and associated adverse events

	Overall use of involved SGA		Use of SGA with contraindicated drug		Use of contraindicated combination without monitoring	Adverse events
	Hospitalizations (n)	Patient-days (n)	Hospitalizations (n)	Patient-days (n)	Hospitalizations (n)	Case description
Potentially interacting drug combinations						
a) Combinations with a labeled contraindication						
Clozapine and drugs that increase the risk of agranulocytosis	114	866	68	349	15	Neutropenia under combined therapy of clozapine with metamizole (neutrophils 1.01 G/l, normal >1.4 G/l). Full recovery to normal values after stop of metamizole.
Quetiapine and CYP3A4 inhibitors	599	4276	30	182	25	Abnormal QTc (463 ms) under combined therapy of quetiapine with voriconazole. Therapy continued, no follow-up ECG.
Amisulpride and drugs with high or moderate potential of QTc-prolongation	22	102	13	72	10	One case identified as part of internal quality management, but no documented consent from patient to publish details from original medical records for research purposes.
Ziprasidone and drugs with high or moderate potential of QTc-prolongation	1	11	1	11	1	0
b) Combinations with a labeled high risk of QT-prolongation without formal contraindication						
Clozapine and drugs with high and moderate potential of QTc-prolongation	115	866	58	388	51	Abnormal QTc (477 ms) under combined therapy of clozapine with quetiapine, sertindole, lithium, amitriptyline and ciprofloxacin. Therapy continued, no follow-up ECG.
Risperidone and drugs with high and moderate potential of QTc-prolongation	170	1214	111	647	100	Abnormal QTc (487 ms) and symptomatic supraventricular extrasystoles under therapy with risperidone 5 hours after intravenous administration of ondansetrone. Normal QTc (435 ms) after stop of ondansetrone.
Paliperidone and drugs with high and moderate potential of QTc-prolongation	13	49	7	31	7	0

3.3.7. Conclusion

The current study analyzed SGA use and associated metabolic profiles and potential drug interactions including their outcomes in a real-life inpatient setting of a tertiary care hospital. We found that 1.6% of all hospitalized patients received SGA, about one third of SGA users were 65 years and older, more than 80% of SGA were prescribed to patients admitted for non-psychiatric primary diagnoses, and that cerebrovascular disorders and heart disease ranked among the top three primary admission diagnoses. These features characterize SGA users in a tertiary care hospital as a high risk population for cardio- and cerebrovascular events and frequent polypharmacy, the latter predisposing to a high risk for drug interactions.[27] Quetiapine and olanzapine accounted for the majority of SGA use, and both are well known to cause metabolic disorders and QT-prolongation. The predominant use of quetiapine is also in line with previous reports.[58,78] and quetiapine is subject to drug interactions with inducers and inhibitors of CYP3A4 drug metabolizing enzymes. Inducers and inhibitors of CYP450 enzymes are frequently used in tertiary care hospitals including e.g. several antiepileptic, antifungal and antibiotic drugs. Aripiprazole with its presumably lower risk for causing adverse metabolic effects was not as frequently used, but it is also subject to interactions via CYP2D6 and CYP3A4, and QT-prolongation is a well-known associated risk. Clozapine accounted for 10% of SGA use, and bone marrow suppression is a major concern in addition to its associated risk of interactions and QT-prolongation. This risk is further elevated in combination with other drugs that may cause neutropenia and agranulocytosis such as metamizole, methotrexate or azathioprine and requires regular blood count monitoring. Ziprasidone and lurasidone, which are comparable to aripiprazole in that they are also considered to have a low risk of metabolic disorders, were not (yet) marketed in Switzerland during the study period.

Furthermore, documented indications suggest that off-label prescriptions account for a major part of SGA use in the studied setting, particularly for sleeping and eating disorders. This is in accordance with other studies in different populations and confirms the common practice of prescribing SGA beyond their labeled indication.[59,60] In some cases off-label use may constitute an avoidable risk and a formal and clinically relevant medication error. However, off-label use as well as the co-prescription of potentially interacting drugs does not necessarily have to be problematic, sometimes even for formally contraindicated drug combinations. In many instances it can be justified if possible risks are thoroughly weighed against benefits, and if there are no alternatives and no clear evidence regarding clinical relevance of risks. Nevertheless, such practice always implies at least an increased burden of responsibility for the prescribing physician and the hospital where it occurs. Therefore, in all those instances at least monitoring for adverse events should be taken seriously. From a

broader perspective the growing number of persons exposed to SGA call for population studies assessing risks vs. benefits of SGA use, also for disorders other than psychosis and for unlabeled use.[57]

Our study provides a two-sided answer to these issues. On the one hand it is reassuring that we identified only five adverse events related to drug interactions with SGA use in our study population over a time of two calendar years, and none of them was irreversible. Given our thorough case-by-case evaluation we also consider it as unlikely that we missed serious adverse drug reactions caused by interactions with SGA during hospitalization. On the other hand, we found that among SGA users with according monitoring the prevalence of hypertension, hyperglycemia, dyslipidemia and BMI ≥30 kg/m² was 36.9, 22.6, 61.1 and 23.1%, respectively, and that of those 37.1, 63.4 and 70.8%, respectively, had no pharmacotherapy for these conditions. Equally important we also found that a large proportion of SGA users had insufficient monitoring regarding adverse metabolic effects and QT-prolongation. Furthermore, if problematic medication is continued, adverse events occurring after discharge may have remained undetected, particularly arrhythmia associated with QT-prolongation and long-term adverse effects of metabolic disorders.[67] Indeed, in our function as a regional pharmacovigilance center we regularly receive reports of avoidable serious and sometimes fatal adverse drug reactions (particularly torsade de pointes tachycardia) associated with drug interactions with SGA, underlining their clinical relevance. Severe adverse effects of SGA and a need for improved monitoring in clinical practice are also documented in the literature. Girardin and colleagues reported fatal cases of arrhythmia associated with SGA in their well-designed prospective study.[79] And a study in a Swiss psychiatric outpatient setting systematically screened SGA users for dyslipidemia and reported a prevalence of 21 to 27%.[80] The low proportion of SGA users that are screened for metabolic abnormalities in the present study is also in line with results from a recent meta-analysis, which found that monitoring of metabolic risks in patients treated with antipsychotic medication is routinely performed in only 69.8 % (blood pressure), 44.3% (glucose), 59.9% (triglycerides) and 41.5% (cholesterol).[66] And in the CATIE landmark trial, 89% of patients with dyslipidemia and 45% of patients with diabetes were untreated.[81]

For the interpretation of our findings, one has to consider some limitations imposed by the data source and study design. We followed patients during hospitalization, but for the time before admission and after discharge we were not able to collect comprehensive information on the duration of SGA use, metabolic profiles and adverse events. Therefore, frequencies of metabolic abnormalities must be seen as cross-sectional prevalence data, whereas no conclusions can be drawn on their incidence and causal relationship in relation to SGA use. Furthermore, some patients may have received SGA only for a short time, which may still be relevant for the risk of QT-prolongation, but less so regarding adverse metabolic outcomes.

In addition prevalent metabolic abnormalities do not always equal an indication for pharmacological treatment. Nevertheless and regardless of these limitations, we must assume that monitoring of the QT interval and/or metabolic parameters, management implications such as glucose and lipid lowering pharmacotherapy or switching to other SGA and avoiding interacting drug combinations would have been indicated in a considerable proportion of SGA users.

From a pragmatic perspective one must realize that it is a challenging task to achieve changes in the prescribing and monitoring of SGA therapy with the aim to avoid critical interactions and adverse effects in clinical practice. However, the introduction of electronic medical records with electronic drug prescription provides new opportunities for efficient and effective clinical decision support. Today we already screen pharmacotherapy for potential medication errors in the electronic medical records at our institution as part of our proactive quality management efforts. We have also started the implementation of semi-automated screening algorithms for specific medication errors into our electronic prescribing system, followed by recommendations on patient management in case of clinical relevance. Implementation of such clinical decision support measures for SGA could help preventing associated adverse effects. Switching to SGA that are less likely to cause metabolic complications in patients with metabolic abnormalities has shown promising results and - if sufficient efficacy can be achieved - should be preferred over adding pharmacological treatment against the metabolic complications, which adds to the patients' drug burden and may compromise their compliance.[62,82,83]

In conclusion, our findings suggest that serious adverse effects of drug interactions with SGA are very rare, but also that a considerable proportion of patients with SGA exposure is neither adequately monitored nor managed, particularly concerning metabolic risks and QT-prolongation. New opportunities through electronic medical records with highly specific electronic clinical decision support may play a key role for proactive safety management of antipsychotic and other pharmacotherapy in the future.

3.4. Benzodiazepine Use During Hospitalization: Automated Identification of Potential Medication Errors and Systematic Assessment of Preventable Adverse Events

3.4.1. Authors

David F. Niedrig, Liesa Hoppe, Sarah Mächler, Heike Russmann, Stefan Russmann

3.4.2. Remarks

Significance for thesis & notable features

This study represents another in-depth analysis of a drug class with a well-known potential for ADE and delivers highly efficient and effective algorithms to detect clinically relevant ME. With a systematic assessment of the preventability of validated ME it provides additional insights for the development of subsequent automated alert algorithms. This study used the administration of a specific antidote (flumazenil) as a surrogate to detect cases with ADE of high clinical relevance. In addition, sophisticated algorithms considered multiple relevant DDI with respect to secondary metabolic pathways of the studied drugs, even if they were administered one or two days before the administration of the studied benzodiazepines.

Contributions of the author of this thesis

David Niedrig contributed to the study design, algorithm development and programming, data compilation and interpretation, and wrote the first version of the manuscript.

Publication

This Study has been submitted as original research for publication to PLOS ONE and is currently in the review process under consideration for publication.

3.4.3. Background

Benzodiazepines and “Z-drug” GABA-receptor modulators (BDZ) are among the most frequently used drugs worldwide.[84-86] Most BDZ have labeled indications for anxiety and sleeping disorders.[86,87] BDZ are also used as add-on therapy for psychiatric disorders, for pre-operative sedation, and for the prevention and treatment of seizures. They are frequently prescribed in hospitals, institutions and community dwelling settings and generally considered safe because of their tolerability and wide therapeutic range.[88,89] According to their summary of product characteristics (SPC), BDZ are not destined for long-term use. However, long-term treatment with BDZ is frequent and may lead to tolerance and addiction.[85,86,90] Tolerance and abuse are well known challenges, for which health authorities and insurances often impose special regulations with regard to BDZ prescribing, dispensing and compensation.[91]

Severe ADE of BDZ, particularly at higher doses, include musculoskeletal weakness with falls and subsequent injuries[92-94], respiratory depression[95-98], paradoxical reactions[99-102], or increased and prolonged CNS depression.[87] If BDZ toxicity is suspected, the antidote flumazenil can quickly antagonize the effects of BDZ, and it can also be used in emergency care to diagnose BDZ overdose.[87] Due to altered pharmacokinetics and increased intrinsic sensitivity, BDZ use can be particularly problematic in elderly and frail patients.[103,104] Restrictive use of BDZ and low dosing at treatment initiation is therefore recommended according to their labels and expert consensus guidelines such as the “Beers” and “Priscus” lists, or the “STOPP” criteria.[105-107] Some drugs may also inhibit the metabolism of BDZ via cytochrome P450 (CYP) enzymes and therefore cause relevant pharmacokinetic drug-drug-interactions (DDI).[108] Concomitant use of strong CYP inhibitors may lead to five- to tenfold increase in BDZ exposure and consequently to dose-dependent adverse drug effects (ADE). Furthermore comorbidities such as acute renal impairment or respiratory disease can render patients more vulnerable to adverse effects of BDZ.

Prevalence of formally inadequate use of BDZ has been studied before.[90,92,109,110] For example Zint et al. found the concomitant use of BDZ with relevant CYP inhibitors to be associated with an increased risk of hip fractures in a community dwelling setting.[92] However, there is a paucity of data on the clinical relevance and preventability of BDZ-related potential medication errors (ME) in tertiary care settings. In such a setting patients may frequently be polymorbid and frail, have additional risk factors for BDZ-induced ADE, and may also be more often exposed to potent CYP inhibitors as compared to patients in other settings.

In order to analyze and improve drug safety in a tertiary care hospital, we created a local pharmacoepidemiological database with data extracted from the hospital’s clinical information system. This setup enables us to perform highly efficient retrospective local

evaluations of potential ME and associated ADE in clinical practice, and subsequently develop recommendations for the effective prevention of ADE.

3.4.4. Objectives

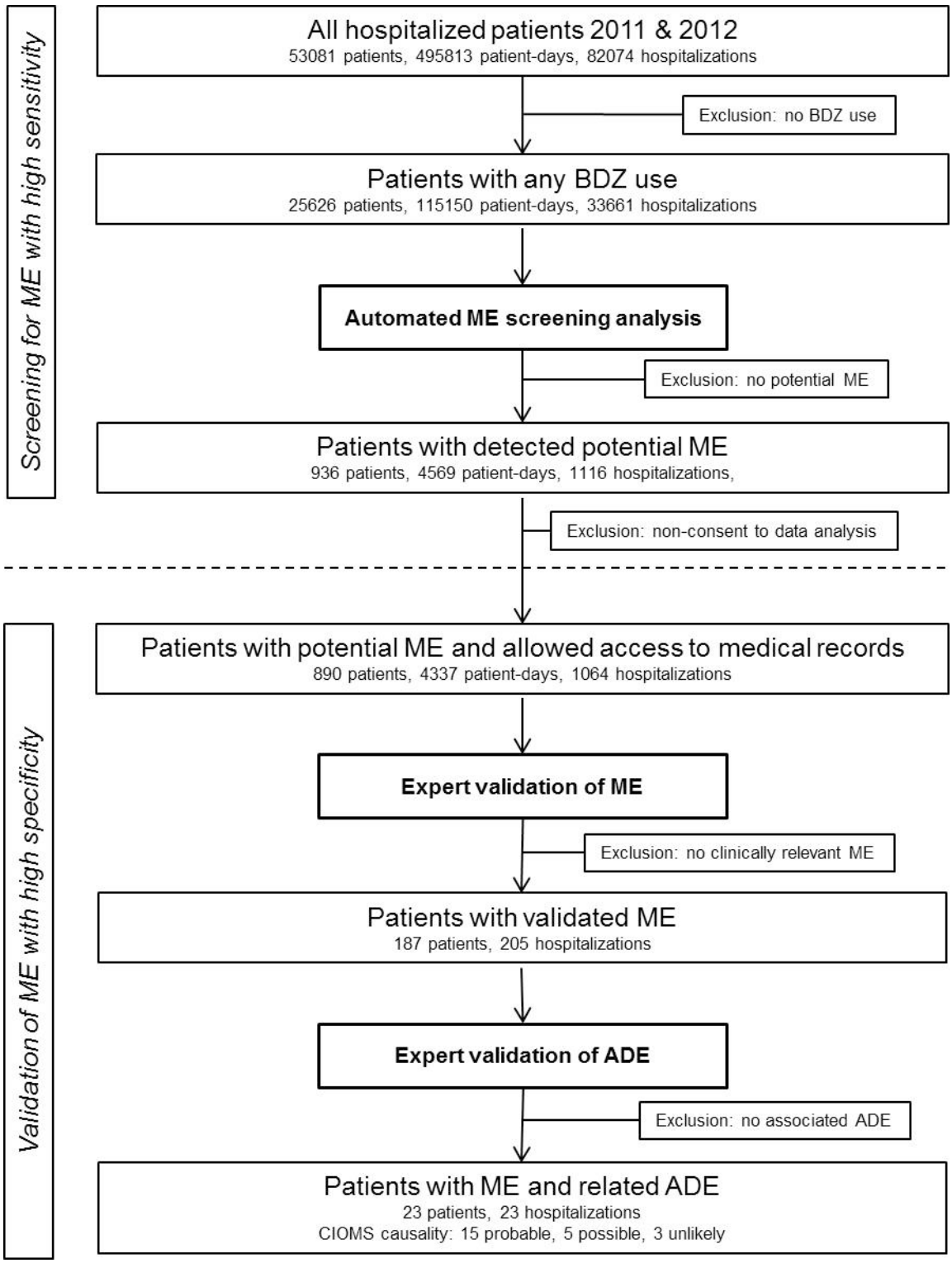
The current study aimed to perform such analyses and quantify the following outcomes: 1. BDZ usage patterns and algorithm-detected potential ME, 2. Validated ME with inappropriate BDZ use in a patient's individual clinical context, 3. Associated ADE.

3.4.5. Methods

Study population, data collection and study design

Selection of the study population and overall study design are presented in **Figure 9**. We conducted a retrospective observational study that analyzed BDZ usage patterns, potential ME, and associated ADE in a tertiary care hospital with about 1000 beds and 40 clinical specialty divisions. The cantonal ethics committee, the hospital's medical director and the hospital's center for clinical research had approved the data extraction, the setup and analysis of the anonymized pharmacoepidemiological database, and the access to original medical records for our research.

Figure 9: Study design and selection of the study population



Data Source

We used our previously described comprehensive pharmacoepidemiological database containing information on demographics, laboratory results and electronic drug prescriptions for hospitalized patients of a Swiss tertiary care hospital covering admissions from the calendar years 2011 and 2012.[111] ICD-10 codes of primary diagnoses were available for the calendar year 2012. For the validation of potential ME and ADE we had access to and reviewed comprehensive electronic medical records.

Prevalence of BDZ use and algorithm-based identification of potential medication errors

We developed and programmed algorithms for the automated detection of patient-days with potential medication errors. Algorithms were customized and validated separately for each studied BDZ. Our analyses focused on frequently used BDZ with potentially relevant interactions via CYP metabolism or with altered pharmacokinetics in renal impairment. Clobazam was not analyzed using automated algorithms because in the studied setting it is predominantly used for treating post-stroke epilepsy and delirium, two conditions where doses are individually titrated.[87] In order to identify BDZ administrations and potentially interacting co-medication we used ATC-codes provided by the WHO.[112] For each BDZ undergoing CYP-metabolism we established a list of relevant CYP inhibitors. These were based on the drugs' summary of product characteristics (SPC) and comprehensive scientific information sources including specialized drug interaction software and websites.[113-116] The final lists only included CYP-inhibiting drugs with a strong effect according to at least one reference. Certain strong CYP 3A4 inhibitors (e.g. clarithromycin) are known to irreversibly bind and inactivate CYP 3A4 enzymes, which results in reduced metabolic capacity until they are synthesized *de novo.*[116,117] Other strong CYP 3A4 inhibitors do not exhibit such a mechanism-based effect (e.g. itraconazole), but their metabolites may continue to inhibit CYP metabolism for some time after cessation.[118,119] Hence administration of strong CYP 3A4 inhibitors was considered potentially relevant if it occurred on the same day or up to two days prior to BDZ administration and thus defined our search algorithms for patient-days on which BDZ administration represented a potential ME. Furthermore, we also identified concomitant use of multiple BDZ, additional relevant CYP inhibitors of CYP 2C19 or 1A2, and co-medication of opioids and muscle relaxants on the same day because those may contribute to BDZ associated ADE.[120-122]

Because severe renal impairment is a formal contraindication to the use of lorazepam according to the Swiss SPC, we developed an algorithm that identified all patients with lorazepam administrations and a current eGFR < 30 ml/min. Furthermore, we also identified and validated any use of the specific BDZ antidote flumazenil as a possible indicator of BDZ-related ME.

Validation of medication errors

For every hospitalization, during which at least one day with a potential ME was identified using the algorithms described above, we validated the clinical context of the BDZ administrations. For that purpose we reviewed the original medical records and compiled the following additional information: indication, dose and route of administration of any BDZ, concomitant use of opioids and muscle relaxants, long-term oxygen therapy before and after BDZ administration, alcohol and substance abuse, relevant severe pulmonary and liver diseases, organ transplantation, renal replacement therapy, and whether the BDZ was administered in a palliative situation. Finally, we assessed the clinical relevance of these parameters for each patient's individual clinical situation and determined whether BDZ administration was a validated ME, i.e. a more cautious or no use of BDZ with alternative therapy would have been indicated under the given circumstances (**Table 4**).

Table 4: Qualitative impact of patient parameters on validation of ME

Parameter	***Impact on assessment of ME***	
Palliative situation	Benefit outweighs risk, no ME	✖
Known BDZ abuse	Tolerance of high BDZ dose, no ME	✖
Low dose of BDZ	≤ 1/2 of standard dose	↓
≥ 1 other BDZ	depending on number & dose	↗
Respiratory insufficiency	If severe	↗
Hepatic impairment	If severe	↗
Age ≥ 65 & dose	If initial dose not reduced	↗

Identification and assessment of adverse drug events

For all validated ME we reviewed comprehensive original medical records for documented associated ADE including falls, severe and prolonged CNS depression, respiratory depression, apnea, paradoxical reactions, hypoxemia and coma. If an associated ADE was documented we assessed the causal relationship using standardized international WHO/CIOMS causality assessment criteria.[2] We also assessed whether the associated ADE may have been prevented if a more cautious BDZ use had been recommended in time to the prescribers - such as an initially lower BDZ dose, omission of additional BDZ, reducing the amount of possible “on demand” BDZ prescriptions, or using a different BDZ without relevant CYP metabolism or one that can be used in renal impairment.

Data analysis

Data analysis was descriptive with presentation of results in tables as appropriate. Frequencieswere calculated with regard to individual patients, hospitalizations and patient-days. Datamanagement and analyses were done using STATA Version 13.1 (STATA Corporation,College Station, TX, USA).

3.4.6. Results

Prevalence of BDZ use

Among a source population of 53081 individual patients contributing 82074 hospitalizations and 495813 patient-days, we identified the study population of all BDZ users. Frequency of BDZ use, demographics and other characteristics of the study population are presented in **Table 5**. BDZ were administered on 23.2% of all patient-days, and at least once in 48.3% of all hospitalized patients and in 41.0% of all hospitalizations. Mean duration of hospitalization was 10 days (median: 5 days). Polypharmacy was frequent: on 42.0% of patient-days with any BDZ use 11 or more additional drugs were administered during hospitalization.
Most frequently coded primary diagnoses for hospitalizations in 2012 with exposure to BDZ were “other forms of heart disease” (I30-I52, 4.1%), “benign neoplasms, except benign neuroendocrine tumors” (D10-D36, 4.1%) and “non-inflammatory disorders of female genital tract” (N80-N98, 3.1%). While lorazepam was the most frequently administered drug regarding patient-days (36.1%), midazolam was the most frequently used BDZ regarding individual patients (58.5%) and hospitalizations (52.1%). Zolpidem and oxazepam were also among the most frequently used BDZ. The use of some BDZ was marginally low, i.e. the combined use of flurazepam, zopiclone, flunitrazepam, clorazepate, lormetazepam, nitrazepam, temazepam, prazepam and ketazolam accounted for only 1.4% of all BDZ administrations. For zolpidem, pharmacokinetics and pharmacodynamics change with age,

and the recommended standard-dose is therefore reduced to 5 mg instead of 10 mg in patients ≥65 years of age. It should only be exceeded if efficacy is insufficient with 5 mg according to the SPC. Therefore, the age- and dose-distributions for zolpidem users are of particular interest. A mildly higher proportion of patient-days with zolpidem use occurred in patients ≥65 years of age compared to all BDZ users (45.8% vs. 41.1%, respectively). Among all patient-days with zolpidem use the daily dose was at least 10 mg per day in 74.2%, but for the subpopulation of patients ≥65 years this was almost as high, i.e. 67.4%. This is equivalent to the impressive absolute number of 10749 days of zolpidem use with a dose ≥10 mg per day in patients ≥65 years in the studied population over two years. Administration of two different BDZ at the same day occurred in 7.1% of patient-days, and 211 patients received three or more different BDZ on the same day, with a maximum of 5 different BDZ. Co-medication with opioids was common (27.2% of patient-days on any BDZ), and on 4.3% of the studied patient-days two or more opioids were administered concomitantly. The departments with the highest proportion of BDZ use were the departments of reproductive endocrinology, diagnostic and interventional radiology, and radio-oncology with BDZ exposure on 45.4%, 34.7% and 33.7% of patient-days, respectively.

Table 5: Characteristics of the study population

	patient-days		*patients*		*hospitalizations*	
	n	*%*	*n*	*%*	*n*	*%*
All patients hospitalized in 2011 & 2012	495813		53081		82074	
Study population						
Administration of ≥ 1 BDZ	115150	100	25626	100	33661	100
Age						
< 18	1037	0.9	677	2.6	803	2.4
18 - 44	23831	20.7	7903	30.8	9701	28.8
45 - 64	42938	37.3	8565	33.4	11632	34.6
65 - 85	42736	37.1	7608	29.7	10450	31.0
> 85	4608	4.0	873	3.4	1075	3.2
Sex						
Male	58566	50.9	12860	50.2	17225	51.2
Female	56584	49.1	12766	49.8	16436	48.8
# of concomitant drugs [I]						
1 - 5	24113	20.9	8419	32.9	11430	34.0
6 - 10	42723	37.1	7530	29.4	10138	30.1
11 - 20	44861	39.0	6360	24.8	9007	26.8
≥ 21	3453	3.0	3317	12.9	3086	9.2
Most frequently administered BDZ [II]						
Lorazepam	41540	36.1	8704	34.0	10753	31.9
Zolpidem	34841	30.3	7150	27.9	8873	26.4
Midazolam	20362	17.7	14993	58.5	17549	52.1
Oxazepam	11370	9.9	2487	9.7	2929	8.7
Clobazam	5285	4.6	617	2.4	760	2.3
Bromazepam	3232	2.8	453	1.8	541	1.6
Diazepam	1736	1.5	324	1.3	402	1.2
Alprazolam	1586	1.4	184	0.7	238	0.7
Clonazepam	1549	1.3	196	0.8	248	0.7
Triazolam	569	0.5	48	0.2	75	0.2
Administration of ≥ 2 different BDZ						
Use of 2 BDZ	8119	7.1	2887	11.3	3339	9.9
Use of 3 BDZ	386	0.3	205	0.8	221	5.9
Use of ≥ 4 BDZ	23	< 0.1	17	0.1	17	< 0.1
Concomitant use of opioids						
Use of 1 opioid	26351	22.9	6505	25.4	7976	23.7
Use of 2 opioids	4953	4.3	1725	6.7	1978	5.9
Use of 3 opioids	16	< 0.1	11	< 0.1	12	< 0.1
Concomitant use of muscle relaxants	1860	1.6	322	1.3	1.3	1.1

[I] Number of concomitant drugs was defined by individual ATC codes.
[II] Considers use of multiple BDZ (benzodiazepines) on same patient-day.

Drug interactions, renal impairment and potential medication errors

We identified 19 different BDZ that were administered in the studied setting of a tertiary care hospital. For 9 of those we identified possible clinically relevant CYP-related DDI, and for lorazepam we identified critical use in severe renal impairment. These patients were further analyzed for according potential ME and are presented in **Table 6**. Overall, our algorithms detected potential ME on 4237 patient-days, occurring during 1066 hospitalizations. This number is equivalent to an average of 5.8 potential ME regarding BDZ administrations on each calendar day in 2011 and 2012. Thereof 3372 patient-days with potential ME were due to concomitant administration of BDZ with strong CYP inhibitors. With the exception of midazolam, BDZ that were used more frequently also contributed more hospitalizations with potential ME. Most were contributed by zolpidem (2555 patient-days, 7.3% of all zolpidem patient-days) and midazolam (440 patient days, 2.2% of all midazolam patient-days). Alprazolam contributed only 191 patient-days but was the BDZ with the highest proportion of potential ME (12.0%). In addition we identified 1197 patient-days with potentially inadequate administrations of lorazepam in patients with severe renal impairment. Analysis of flumazenil use identified 15 patient-days (occurring during 13 hospitalizations) with potential ME related to BDZ use.

Our algorithms detected sporadic patient-days with exposure to numerous studied drugs, e.g. patients concomitantly receiving 2 BDZ *and* 2 strong CYP 3A4 inhibitors *and* 2 opioids *and* a muscle relaxant. Other patients received up to 510 mg zolpidem per day, but according to the medical records very high doses were prescribed intentionally in patients with severe BDZ addiction, and we therefore did not classify those as ME.

Table 6: Algorithm-based identification of potential ME

	Mechanism for potential ME	***BDZ total use***		***Potential ME***			
		patient-days	*hospitalizations*	*patient-days*	*%*	*hospitalizations*	*%*
Zolpidem	Co-medication with ≥ 1 strong CYP 3A4 inhibitor	34841	8873	2555	7.3	493	5.6
Midazolam[I]		1401 /18989	17549	108 / 332	7.7 / 1.7	192	2.5
Diazepam		1736	402	106	6.1	15	3.7
Alprazolam		1586	238	191	12.0	16	6.7
Triazolam		569	75	9	1.6	3	4.0
Zopiclone		498	93	9	1.8	2	2.2
Flunitrazepam		349	75	38	10.9	7	9.3
Clorazepate		202	31	9	4.5	1	3.2
Nitrazepam		145	20	0	-	0	-
Prazepam		48	9	0	-	0	-
Lorazepam	Severe renal impairment[II]	41540	10753	1197	2.9	324	3.0
Flumazenil	BDZ antidote (surrogate for BDZ overdose)	15	13	15	100.0	13	100.0

[I] Patient-days with p.o. / i.v. administration; hospitalizations with any i.v. or p.o. midazolam administration

[II] In order to qualify as potential ME, in addition to eGFR < 30 ml/min, patients hat to EITHER receive lorazepam on ≥ 2 consecutive days OR to also have had co-administered ≥ 1 additional BDZ

Validation of medication errors

For 1064 available hospitalizations we assessed the clinical relevance of algorithm-identified potential ME. After consideration of the patients' individual clinical situation we classified 205 of those (19.3%) as validated ME (**Table 7**). Hospitalizations with potential ME concerning lorazepam use in severe renal impairment were classified as validated ME in 41.4%. Among potential ME in hospitalizations with exposure to zolpidem and strong CYP inhibitors, 56 (11.4%) were classified as validated ME. Most cases were assessed as clinically relevant due to pre-existing respiratory insufficiency and old age. Among hospitalizations with potential ME concerning midazolam, which is frequently administered only once before interventions, only 6.3% were confirmed as validated ME. For three hospitalizations with a potential ME concerning triazolam, all were confirmed as ME while none out of 15 potential ME with diazepam appeared clinically relevant, mostly because the patients were known drug addicts. Similarly, the assessment of the clinical context of potential ME with zopiclone, flunitrazepam and clorazepate did not contribute any validated ME.

Table 7: Potential- and validated ME and associated ADE

	hospitalisations		***≥ 1 other BDZ***	***≥ 1 opioid***	***Indication [I] (n)***	***Presence of risk factors (n)***			***ADE [II]***
	n	*%*	***(n)***	***(n)***	*sleep / anx / inv / unkn*	*respiratory insufficiency*	*severe liver disease*	*Age ≥65*	***(n)***
Zolpidem potential ME	**493**	**100**							
no ME	437	88.6	54	93	432 / 2 / 2 / 1	169	87	109	n.a.
validated ME	56	11.4	6	10	55 / 0 / 0 / 1	27	6	38	11
validated ME & associated ADE	11	2.2	1	2	11 / 0 / 0 / 0	5	0	5	-
Midazolam potential ME	**192**	**100**							
no ME	180	93.8	47	51	6 / 24 / 145 / 5	52	18	34	n.a.
validated ME	12	6.3	6	6	11 / 0 / 0 / 0	3	1	7	1
validated ME & associated ADE	1	0.5	0	1	1 / 0 / 0 / 0	0	0	1	-
Triazolam potential ME	**3**	**100**							
no ME	0	-	-	-	-	-	-	-	n.a.
validated ME	3	100.0	1	1	3 / 0 / 0 / 0	1	0	2	1
validated ME & associated ADE	1	33.3	0	0	1 / 0 / 0 / 0	1	0	0	-
Lorazepam potential ME	**324**	**100**							
no ME	190	58.6	65	77	99 / 77 / 1 / 13	48	44	106	n.a.
validated ME	134	41.4	25	39	100 / 31 / 1 / 2	49	27	82	10
validated ME & associated ADE	10	3.1	4	6	7 / 3 / 0 / 0	3	1	8	-

[I] Indication: anx = anxiety / inv = pre-invasive / unkn = unkown

[II] ADE = adverse drug event

Identification and assessment of adverse drug events

In the 205 hospitalizations where a validated ME had occurred we systematically searched the original medical records for related ADE. This revealed 23 patients with ADE compatible with intrinsic effects of BDZ, i.e. falls, prolonged CNS depression and dyspnea (**Table 8**). According to WHO/CIOMS causality assessment 15 of the ADE had a “probable”, 5 a “possible” and 3 an “unlikely” causal relation to the respective BDZ ME. Of the 10 ADE associated with lorazepam, 8 occurred in elderly patients and 7 were found to be preventable if a more cautious use such as no co-administration of additional BDZ had been respected. Of the 11 ADE associated with zolpidem, 6 occurred in patients ≥65 years and 9 were found to be preventable. According to CIOMS criteria, the ADE associated with midazolam was assessed as ‘probable’ and preventable. On the other hand, causality of the ADE with tetrazepam was assessed as ‘possible’ and found not to be preventable during hospitalization, as BDZ administration and the ADE had actually occurred before admission. Finally, the identification of all flumazenil administrations in our dataset revealed four cases of severe ADE resulting from inadequate BDZ administrations (**Table 8)**. In two of those preventable ME strong CYP inhibitors had been co-administered with BDZ while in one case lorazepam had been administered in a patient with severe renal impairment (eGFR of 18 ml/min). Additional relevant CYP inhibitors and administration of multiple BDZ were also present in all four cases.

Table 8: Cases with severe ADE

	total number ADE	***Fall***		***CNS depression***		***eGFR[I] <30 ml/min***	***CIOMS***			***Presence of risk factors***			***Preventable***	
		minor injury	*major injury[II]*	*→ with respir. depression*			*unlikely*	*possible*	*probable*	*respiratory insufficiency*	*severe liver disease*	*age ≥65*	*yes*	*no*
Zolpidem	11	5	2	4	2	1	2	1	8	5	-	5	9	2
Midazolam	1	1	-	-	-	-	-	-	1	-	-	1	1	-
Triazolam	1	-	1	-	-	-	-	1	-	1	-	-	-	1
Lorazepam	10	4	4	2	2	10	1	3	6	3	1	8	7	3
Flumazenil	4	-	1	3	1	1	-	-	4	2	-	2	4	-

[I] eGFR = estimated glomerular filtration rate according to CKD-EPI

[II] Thereof four with subsequent emergency CT scans and one other case with fracture of femur

3.4.7. Conclusion

Our study analyzed BDZ usage patterns, potential medication errors and associated ADE in the real-life setting of a tertiary care university hospital. In order to perform such analyses we had previously extracted electronic drug prescriptions, renal function measures and other clinical data from the database of an existing electronic clinical information system and set up a local pharmacoepidemiological database. This step is essential for two reasons. First, a rational allocation of limited available resources to improve hospital drug safety requires systematic retrospective real-life data on the frequency of preventable ME, and the usually much lower frequency of resulting severe ADE. Besides, nothing is as convincing to local prescribers and decision makers as being challenged by opportunities for improvement based on real local ME. Second, the setup of such a database requires an interface with the local clinical information system. This is a necessary prerequisite for the development of real-time analyses and alerts that can be returned through the same interface to local safety experts and prescribers. Only such systems may eventually offer the necessary efficiency and efficacy in order to have a measurable impact on patient safety in clinical practice.

For the currently studied drug class of BDZ we found that their use as well as the risk for drug interactions was even higher than we had expected. Approximately one out of two patients received at least once a BDZ during hospitalization. Concomitant exposure to multiple BDZ is rarely justified but was detected in 7% of patients. And polypharmacy with more than 10 additional concomitant drugs was present in 42% of patient-days.

At the same time one has to realize that midazolam contributed 17.7% of patient-days with BDZ use, but midazolam was frequently only administered as a single intravenous dose before smaller diagnostic or therapeutic procedures. Of note, midazolam drug interactions with CYP inhibitors are much less important for intravenous as compared to oral administration with pronounced first-pass metabolism.[87,108]

For each studied BDZ, we applied an individually programmed algorithm that detected patient-days with potential ME. In addition to the co-administration of strong CYP 3A4 inhibitors, some patients were exposed concomitantly to inhibitors of CYP 2C19 or CYP 1A2. This may further reduce the capability to metabolize certain BDZ, (i.e. diazepam, clorazepate and prazepam for 2C19; zolpidem for 1A2) through the

inhibition of a relevant metabolic bypass.[72,86] Furthermore, the concomitant use of multiple opioids may further enhance CNS-related ADE of BDZ.[120] Algorithm-based detection of potential ME was highly efficient, but only clinically relevant prescribing errors should be considered as true ME and this distinction requires additional manual expert evaluation of individual patients using weighted information from non-structured data. Adapted dosing (i.e. less than half of the recommended dose), palliative situations, or known tolerance of high BDZ doses were the most frequent reasons why potential ME were considered as clinically irrelevant. At the other end of the spectrum current contraindicated conditions (e.g. severe respiratory failure), co-administration of multiple additional BDZ and lack of adaptation of the initial dose in elderly patients were the most frequent reasons why we assessed a potential ME as clinically relevant. Although there is no gold standard for such an expert validation, we consider it as the best available method, and we have successfully applied and evaluated it in prospective studies and ward rounds with instant feedback from the prescribers and subsequent medication changes.[27,33]

Even a true ME does not always result in a severe ADE, and although the proportion of ME that actually result in severe ADE is most important from a clinical point of view, this quantitative aspect is vastly understudied in drug safety research. Therefore, our study systematically searched for and quantified ADE following all validated ME. As expected, only a small proportion of ME led to severe ADE, but over a 2-year period we were able to identify the total number of 20 severe ADE following erroneous administrations of zolpidem, midazolam, triazolam or lorazepam with a formal causality assessment suggesting a causal role for these BDZ. Prospective screening for the underlying ME with our automated algorithms would have detected those, and timely alerts could therefore have effectively prevented them with high efficiency.

Furthermore, we also identified and assessed 15 patient-days with flumazenil administration, which revealed 4 cases of BDZ related ME that caused severe ADE requiring such antidote treatment. Three of those would indeed have been detected in time by our algorithms, which identified co-administration of strong CYP inhibitors in two cases, and relevant renal impairment with an eGFR < 30 ml/min and concomitant exposure to an additional BDZ in another case. Only the remaining fourth case with flumazenil administration would not have been detected by our algorithms due to the lack of exposure to any strong CYP inhibitors. It involved the BDZ oxazepam and alprazolam concomitantly administered with the CYP 3A4 inhibitor fluconazole, which is considered to be only a moderate CYP 3A4 inhibitor.[72,113] All four flumazenil cases could likely have been prevented by either

choosing a lower dose of the involved BDZ or by using BDZ which are not affected by CYP inhibition. Of note, a study in a Brazilian Teaching hospital analyzed the use of flumazenil in patients exposed to intravenous midazolam and interacting drugs.[123] They identified 23 patients exposed to clinically significant drug-drug interactions requiring administration of flumazenil during one year. Most of the cases were related to CNS depressing drugs such as opiates, whereas none were related to CYP 3A4 inhibitors, for which an interaction is much more pronounced if midazolam is administered orally.

Although our study focused on identifiable ME with BDZ one should also realize the very high absolute use of BDZ in the studied setting, and that ADE to BDZ may also occur without preceding ME. Further interventions should therefore also promote a generally more restrictive use of BZD use particularly in elderly patients and are supported by expert consensus guidelines such as the “Beers” and “Priscus” lists, or the “STOPP” criteria.[87,105-107]

Furthermore, our results showed that compliance with dose-adaptation recommendations for zolpidem in elderly patients is very low, i.e. two thirds of zolpidem users receive ≥10 mg/day. In combination of the high prevalence of zolpidem use this resulted in the remarkably high absolute number of 10749 patient days with ≥10 mg of zolpidem use per day in patients ≥65 years over two years in a tertiary care hospital. An analysis of ADE resulting from all high zolpidem doses in elderly patients was beyond the scope of the current study, but our personal experience from safety ward rounds shows that most prescribers are not aware of recommended dose adaptations for zolpidem in elderly patients and readily change the dose when this is brought to their attention.

In conclusion BDZ use was remarkably high in the studied setting of a tertiary care hospital. Our algorithms are able to identify potential ME for BDZ prescriptions through an automated analysis of interacting co-medication and impaired renal function with high efficiency. Although this was done retrospectively in the current study, our next aim is the implementation of prospective real-time screening algorithms for ME that issue immediate alerts. We found that about 20% of potential ME for BDZ prescriptions identified through our automated search algorithms were assessed as clinically relevant, i.e. BDZ prescriptions should have been changed. This further selection of clinically relevant ME still requires manual expert evaluation with a review of patients’ clinical situation and individual risk-benefit evaluation. However, if an automated algorithm performs the screening it would be an easy task for a trained expert to review the approximately 6 alerts that would be generated per

day and subsequently recommend prescription changes in 1 to 2 patients per day. Although serious ADE following ME with BDZ are fortunately rare, our findings indicate that such a system may prevent approximately 10 severe ADE per year in a tertiary care hospital. This absolute number is clinically relevant and may stand in a favorable relation to the resources that are required for the maintenance of a semi-automated proactive safety surveillance system. In addition, automated alerts for dose reduction of zolpidem in elderly patients and a generally more restrictive use of BZD may also prevent a considerable number of BDZ-related ADE and should be further investigated in future studies.

3.5. Drug Safety of Macrolide and Quinolone Antibiotics in a Tertiary Care Hospital: Administration of Contraindicated Comedication and QT-Prolongation

3.5.1. Authors

David F. Niedrig, Sarah Mächler, Liesa Hoppe, Natascia Corti, Helen Kovari, Stefan Russmann

3.5.2. Remarks

Significance for thesis & notable features

While basically similar to the previous two studies, this study considers potential ME related to drug-disease interactions and includes relative overdosing in patients with renal impairment. Using structured information about the patients' current and past diagnoses, i.e. codes of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), it contributed to the identification of patients at risk of clinically relevant ME. However, using these codes needs careful consideration about their timing and overall quality since they are principally used as a administrative instrument for the hospital to request compensation from the insurance companies. Additionally this study focused on certain potential ME that are highly likely to be of clinical relevance due to very pronounced pharmacokinetic DDI.

Contributions of the author of this thesis

David Niedrig contributed to the study design, algorithm development and programming, manuscript writing, data compilation and interpretation, and wrote the first version of the manuscript.

Publication

This Study has been accepted for publication as original research in the European Journal of Clinical Pharmacology in March 2016.

3.5.3. Background

Macrolide and quinolone antibiotics (MQAB) are among the most frequently prescribed drugs that are associated with life-threatening torsade de pointes (TdP) cardiac arrhythmia.[124-128] Information on the assessment of their potential risk to cause TdP vs. therapeutic benefits are featured in their Summary of Product Characteristics (SPC) and other resources such as guidelines, websites and clinical decision support software.[87,129] Patients' resilience to drug-induced TdP is often described as 'repolarization reserve', referring to the ventricle's capacity to compensate delayed repolarization.[130] Prolongation of the QT-interval is an important predictor of TdP, and ECG monitoring is therefore indicated in patients exposed to QT-prolonging drugs with a high risk of TdP. The risk is partially dose-dependent and highest in patients with concomitant administration of several QT-prolonging drugs. Indeed, in clinical practice patients with drug-associated TdP had typically been exposed to several risk drugs. TdP is also associated with additional factors including high age, female sex, hypokalemia, heart diseases and renal impairment.[131-133] If the QTc interval exceeds 500 ms or there is a drug-associated increase by more than 60 ms, QT-prolonging drugs should usually be discontinued.[134] However the risk of TdP may already be increased at QTc intervals above the upper limit of normal, which is commonly defined as 450 ms for men and 460 ms for women.[135] Inpatients of a tertiary care hospital may frequently feature reduced repolarization reserves due to polypharmacy and other risk factors for TdP. Therefore, awareness of TdP-inducing drugs and careful ECG monitoring are important parts of proactive drug safety management in this population.[136]

Furthermore, some MQAB are also well known for avoidable pharmacokinetic DDI.[47,137] Clarithromycin, erythromycin and ciprofloxacin are strong inhibitors of cytochrome P450 isoenzymes (CYP). Their co-administration with certain substrates may outweigh any potential benefits, especially if 'victim-drugs' are prescribed in high doses and if therapeutic alternatives are available. The latency time of resulting adverse drug reactions (ADR) has a broad range. DDI with MQAB may lead to simvastatin-induced rhabdomyolysis only after several weeks of co-administration,[138-140] whereas ciprofloxacin may cause a 7- to 10-fold increase of tizanidine c_{max} and AUC within 24 hours and result in severe hypotension and reduced psychomotor functions.[141]

3.5.4. Objectives

The present study aimed to quantify co-administration of MQAB with QT-prolonging and other potentially interacting drugs, relevant risk factors and the frequency of associated adverse events in the real-life setting of hospitalized patients.

3.5.5. Methods

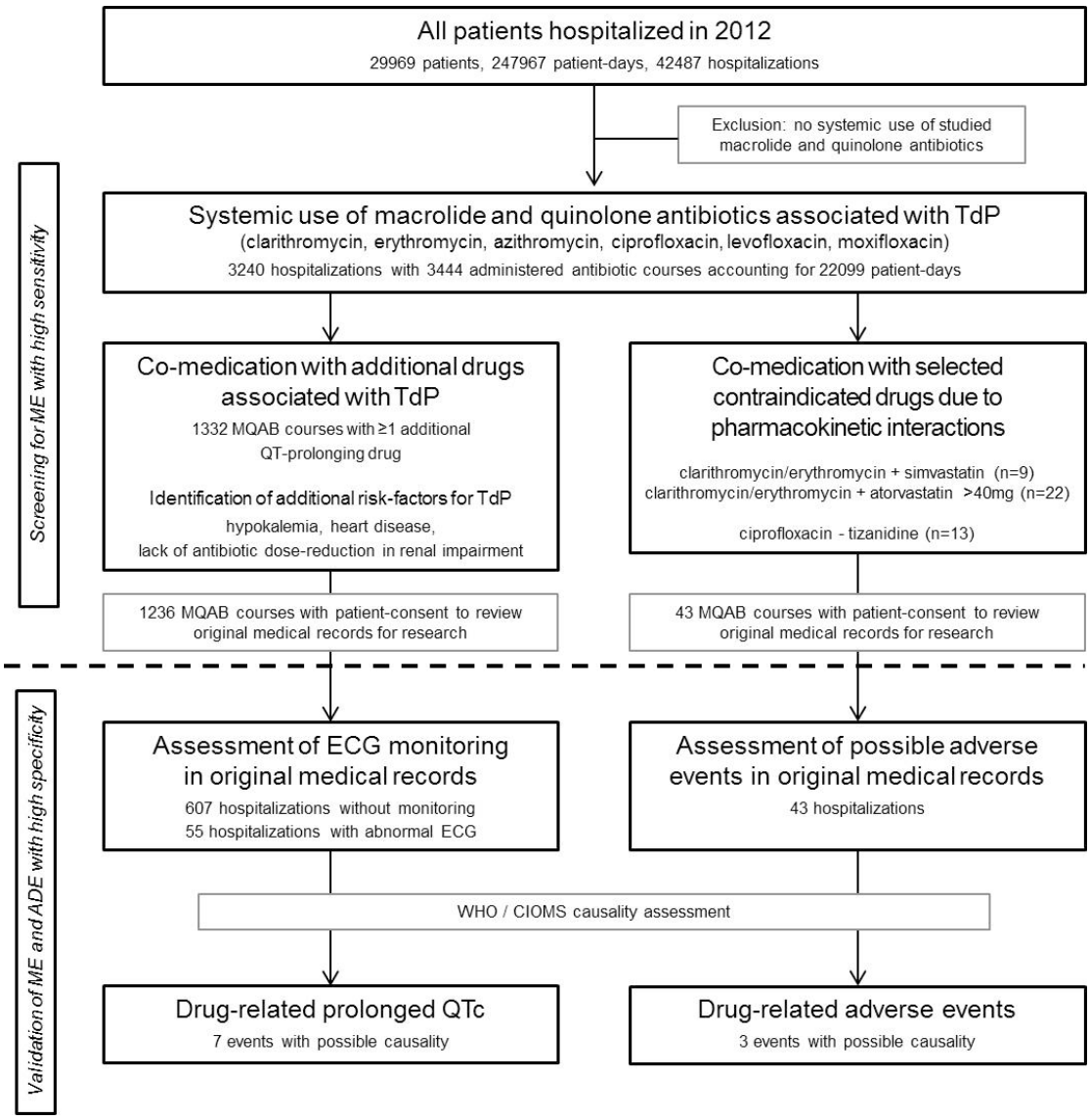
Data Source

The study was conducted using data from the calendar year 2012 of our previously described comprehensive pharmacoepidemiological hospital database.[111] The database contains information on electronic drug prescriptions, demographics, laboratory results and diagnoses for hospitalized patients of a Swiss tertiary care hospital. For the assessment of ECG monitoring and outcome validation of potential DDI we reviewed original electronic medical records unless patients had refused consent to use their data for research upon admission.

Study design

Selection of the study population and overall study design are presented in **Figure 10**. We conducted a retrospective observational study that analyzed usage patterns, ECG monitoring, potential DDI, laboratory data and relevant comorbidities in MQAB users of a tertiary care hospital. The cantonal ethics committee, the hospital's medical director and the hospital's center for clinical research had approved the data extraction, the setup and analysis of our anonymized pharmacoepidemiological database, and the access to original medical records for our research studies.

Figure 10: Study flowchart



Usage patterns of QT-prolonging MQAB, co-administration of potentially interacting drugs and risk-factors for TdP

For the present study we developed, programmed and validated algorithms that searched our database for patients, patient-days and hospitalizations with exposure to MQAB and co-administered drugs of interest. Few hospitalizations with administration of two or more of the studied MQAB contributed to more than one exposure group and were accordingly counted more than once. We analyzed the following MQAB based on their established high potential to cause TdP according to information from their SPC and additional scientific resources:[72,75,87,142,143] ciprofloxacin, clarithromycin, erythromycin, azithromycin, levofloxacin and moxifloxacin. For all users of those MQAB we identified additional co-administered drugs that also have an established high risk for QT-prolongation and TdP. Furthermore we identified selected drugs with well-documented relevant CYP-mediated pharmacokinetic interactions with the respective MQAB, i.e. concomitant administration of clarithromycin or erythromycin with simvastatin or high-dose atorvastatin (≥ 40 mg/d), and combined use of ciprofloxacin with tizanidine. Further algorithms identified additional risk factors for TdP. Current hypokalemia below 3.3 mmol/l or renal impairment with a decreased eGFR[144] that requires dose-reduction for clarithromycin, erythromycin, ciprofloxacin and levofloxacin. For patients with renal impairment we evaluated whether recommended dose-adjustments of the respective MQAB had actually been made.[145] Furthermore, we identified relevant cardiac comorbidities that may increase the risk of TdP based on documented ICD-10 codes of the following heart diseases: heart failure, cardiomyopathy, angina pectoris, myocardial infarction, heart murmurs, aortic stenosis, coronary artery stenosis, cardiac failure, QT prolongation, pacemaker implantation, ventricular septum defect, coronary interventions, palpitations, atrial fibrillation or flutter, supraventricular arrhythmia, tachycardia, and tachy-bradycardia.[126]

ECG-monitoring and evaluation of adverse events associated with potential medication errors

We assessed monitoring for QT-prolongation by reviewing all documented ECGs in patients' original medical records performed up to one week before (baseline) or during the co-administration of potentially interacting drugs for each hospitalization. A corrected QT interval (QTc) of >450 ms in men and >460 ms in women is associated with increased cardiovascular mortality and defined as the upper limit of normal by the American Heart Association. Longer QTc-intervals were accordingly categorized as 'abnormal QTc' for the present study.[135,146] A QTc-interval above 500

ms significantly increases the risk of TdP and sudden cardiac death, and was defined as 'long QTc'.[134] For patients with abnormal and long QTc-intervals we reviewed the original ECG and comprehensive medical records for other, not drug-related contributing QTc-prolonging factors such as pacemakers, left bundle branch blocks or presence of tachycardia (heart rate >100/min). Only if no such confounders were identified, we assessed the causal relationship with the respective QT-prolonging drugs according to standardized WHO/CIOMS causality assessment criteria.[2]
For the studied pharmacokinetic DDI involving simvastatin and atorvastatin we identified symptoms, signs and diagnoses of myopathy in comprehensive medical records including laboratory results of creatine kinase (CK) measurements.[145] For interactions involving tizanidine we evaluated any documentation of hypotension, drowsiness and reduced psychomotor functions.[145]

Data analysis

Data analysis was descriptive with presentation of results in tables as appropriate. Frequencies were calculated with regard to individual patients, hospitalizations and patient-days. Data management and analyses were performed with STATA Version 13.1 (STATA Corporation, College Station, TX, USA).

3.5.6. Results

Characteristics of the study population

Among 29969 patients from our database that had been hospitalized in 2012, 9777 (32.6%) had received treatment with systemic antibiotics. Amoxicillin-clavulanic acid was by far the most frequently used antibiotic (n=4112, 42.1 %), and 29.1 % of patients with systemic antibiotic treatment had received MQAB associated with TdP. Characteristics of the studied MQAB users and frequency distribution of different MQAB are presented in **Table 9**. Ciprofloxacin was the second most frequently used antibiotic in the hospital (19.2% of all patients with systemic antibiotic treatment) and by far the most frequently used MQAB. Mean and median duration of hospitalization for MQAB users were 19.2 and 5 days.

Table 9: Characteristics of the study population

	Hospitalizations		*Patient-days*	
	n	(%)	*n*	(%)
All analyzed MQAB users	**3240**	**100**	**20721**	**100**
Sex				
Male	1913	59.0	12296	59.3
Female	1327	41.0	8425	40.7
Age distribution				
<18	14	0.4	69	0.3
18-44	694	21.4	4106	19.8
45-64	1195	36.9	8537	41.2
65-84	1205	37.2	7272	35.1
≥85	132	4.1	737	3.6
Use of studied antibiotics				
Macrolides				
Clarithromycin	476	14.7	4238	20.5
Erythromycin	184	5.7	901	4.3
Azithromycin	113	3.5	725	3.5
Quinolones				
Ciprofloxacin	2247	69.4	12989	62.7
Levofloxacin	321	9.9	2389	11.5
Moxifloxacin	103	3.2	857	4.1
Units with highest use of MQAB				
Urology	677	20.9	2366	11.4
Viszeral- and transplantation surgery	386	11.9	1895	9.1
Internal medicine	381	11.8	1601	7.7
Pneumology	271	8.4	3671	17.7
Haematology	170	5.2	1551	7.5
Most frequent primary ICD-10 diagnoses				
Malignant neoplasms of lymphoid, hematopoietic and related tissue C81-C96	177	5.5	-	-
Complications of surgical and medical care, not elsewhere classified T80-T88	151	4.7	-	-
Other diseases of the urinary system N30-N39	142	4.4	-	-
Influenza and pneumonia J09-J18	139	4.3	-	-
Malignant neoplasms of digestive organs C15-C26	127	3.9	-	-

Co-medication of MQAB with additional QT-prolonging drugs, other risk factors for TdP and dose-adjustment in renal impairment

Co-medication of MQAB with other QT-prolonging drugs and prevalence of additional risk factors for TdP are presented in **Table 10**. Among 3444 courses of administered MQAB, additional drugs known to cause TdP were administered in 1332 (38.7 %). In 14.2 % even two or more additional QT-prolonging drugs were administered. Some patients received up to 6 drugs known to cause TdP on the same day, frequently involving antiemetics, azole-antifungals and antidepressants. Patients using clarithromycin, azithromycin, levofloxacin or moxifloxacin were more frequently exposed to at least one additional drug known to cause TdP (between 51.5 and 60.4 %) than patients receiving erythromycin (29.9 %) or ciprofloxacin (30.3 %). Current hypokalemia below 3.3 mmol/l, an important risk factor for TdP, was documented in 15.9 %. For users of clarithromycin, erythromycin, ciprofloxacin and levofloxacin lack of recommended dose reduction of MQAB in the presence of impaired renal function was found in 122 (3.8 %) of administered courses. These occurred in 91 hospitalizations with ciprofloxacin (daily doses of >500 mg while eGFR <30ml/min or >1000 mg while eGFR 30-60 ml/min), in 16 hospitalizations with clarithromycin (daily doses of >500 mg while eGFR <30 ml/min), and in 15 hospitalizations with levofloxacin (daily doses of >250 mg while eGFR <20 ml/min or >500 mg while eGFR 20-50 ml/min). Approximately one in three patients exposed to the studied MQAB had a documented ICD-10 diagnosis of heart diseases associated with an increased risk for TdP.

Table 10: Prevalences of QT-prolonging comedication and other risk factors for TdP in MQBA users

	Clarithromycin				Erythromycin				Azithromycin				Ciprofloxacin				Levofloxacin				Moxifloxacin			
	Hospitalizations		Patient-days		Hospitalizations		Patient-days		Hospitalizations		Patient-days		Hospitalizations		Patient-days		Hospitalizations		Patient-days		Hospitalizations		Patient-days	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Use of antibiotic	476	100	4238	100	184	100	901	100	113	100	725	100	2247	100	12989	100	321	100	2389	100	103	100	857	100
Co-medication with at least one QT-prolonging drug	282	59.2	3163	74.6	55	29.9	223	24.8	67	59.3	561	77.4	681	30.3	3923	30.2	194	60.4	1165	48.8	53	51.5	570	66.5
Co-medication with two or more QT-prolonging drugs	166	34.9	2541	60.0	27	14.7	72	8.0	37	32.7	243	33.5	174	7.7	1271	9.8	58	18.1	198	8.3	28	27.2	256	29.9
Most frequently used QT-prolonging co-medication																								
Escitalopram	17	3.6	345	8.1	2	1.1	9	1.0	5	4.4	25	3.4	75	3.3	395	3.0	6	1.9	43	1.8	2	1.9	24	2.8
Fluconazole	17	3.6	30	0.7	10	5.4	23	2.6	0	0.0	0	0.0	72	3.2	311	2.4	33	10.3	93	3.9	6	5.8	14	1.6
Ondansetron	28	5.9	99	2.3	23	12.5	61	6.8	13	11.5	62	8.6	221	9.8	489	3.8	119	37.1	687	28.8	5	4.9	24	2.8
Domperidone	185	38.9	2446	57.7	22	12.0	87	9.7	56	49.6	495	68.3	269	12.0	2192	16.9	63	19.6	324	13.6	32	31.1	347	40.5
Clarithromycin	-	-	-	-	1	0.5	1	0.1	3	2.7	3	0.4	43	1.9	759	5.8	11	3.4	37	1.5	23	22.3	323	37.7
Azithromycin	3	0.6	3	0.1	1	0.5	1	0.1	-	-	-	-	18	0.8	137	1.1	2	0.6	6	0.3	6	5.8	47	5.5
Itraconazole	131	27.5	2460	58.0	2	1.1	2	0.2	0	0.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ciprofloxacin	43	9.0	759	17.9	14	7.6	45	5.0	18	15.9	137	18.9	-	-	-	-	13	4.0	18	0.8	3	2.9	3	0.4
Erythromycin	1	0.2	1	< 0.1	-	-	-	-	1	0.9	1	0.1	14	0.6	45	0.3	0	0	0	0	0	0	0	0
Mirtazapine	20	4.2	131	3.1	7	3.8	35	3.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Levofloxacin	11	2.3	37	0.9	0	0	0	0	2	1.8	6	0.8	13	0.6	18	0.1	-	-	-	-	0	0	0	0
Moxifloxacin	23	4.8	323	7.6	0	0	0	0	6	5.3	47	6.5	3	0.1	3	0	0	0	0	0	-	-	-	-
Hypokalemia (<3.3 mmol/l)[1]	110	23.1	474	11.2	16	8.7	65	7.2	18	15.9	40	5.5	321	14.3	1406	10.8	58	18.1	162	6.8	24	23.3	61	7.1
Renal impairment with need for MQAB dose reduction[2]	87	18.3	724	17.1	2	1.1	2	0.2	-	-	-	-	660	29.4	3723	28.7	67	20.9	347	14.5	-	-	-	-
→ without recommended dose-reduction	16	3.4	29	0.7	0	0	0	0	-	-	-	-	91	4.0	236	1.8	15	4.7	54	2.3	-	-	-	-
ICD-10 diagnosis associated with elevated TdP risk	232	48.7	-	-	24	13.0	-	-	40	35.4	-	-	679	30.2	-	-	108	33.6	-	-	35	34.0	-	-

[1] K+ < 3.3 mmol/l on day(s) of co-administration

[2] For clarithromycin if eGFR < 30 ml/min, for erythromycin if eGFR < 10 ml/min, for ciprofloxacin eGFR < 30 - 60 ml/min, for levofloxacin if eGFR < 20 - 50 ml/min

ECG-monitoring in patients at risk for TdP

For 1332 administered MQAB courses with at least one additional QT-prolonging drug, medical records including performed ECGs could be further reviewed for 1236 (92.8 %). Frequencies of ECG-monitoring and further risk factors for TdP in those patients are presented in **Table 11**. In 50.9 % adequate ECG monitoring was documented. Among patients with adequate ECG monitoring and abnormal QTc (n= 55), patients with non-drug causes for ECG abnormalities (n= 28), or patients with an ECG performed before exposure to the DDI (n= 12) were excluded from the CIOMS causality assessment. Thereafter 15 individual patients with an abnormal / long QTc interval remained for formal causality assessment. For 7 patients with QTc between 478 and 518 ms causality of the involved drugs known to prolong QT interval and cause TdP interval was classified as ‘possible’, and further details are presented in **Table 12**. We identified no episodes of TdP.

Table 11: ECG-monitoring in MQAB users at risk of TdP

	Macrolides						Quinolones					
	Clarithromycin		**Erythromycin**		**Azithromycin**		**Ciprofloxacin**		**Levofloxacin**		**Moxifloxacin**	
	Hospitalizations		Hospitalizations		Hospitalizations		Hospitalizations		Hospitalizations		Hospitalizations	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Co-medication with at least one QT-prolonging drug[1]	259	100	48	100	65	100	632	100	180	100	52	100
--> Thereof adequate QT monitoring: current / pretreatment ECG available[2]	128	49.4	27	56.3	21	32.3	334	52.8	92	51.1	27	51.9
--> Thereof administration during episode(s) of hypokalemia[3]	37	14.3	7	14.6	6	9.2	79	12.5	21	11.7	10	19.2
--> Thereof with ICD-10 codes predisposing for TdP	70	27.0	9	18.8	11	16.9	483	76.4	40	22.2	12	23.1
--> Thereof with renal insufficiency requiring dose adaptation	19	7.3	1	2.1	na	na	123	19.5	14	7.8	na	na
--> Thereof with supratherapeutic dosing	1	0.4	0	0	na	na	7	1.1	3	1.7	na	na
--> Thereof abnormal / long QT[4]	9	3.5	2	4.2	2	3.1	36	5.7	6	3.3	0	0
--> Thereof non-drug-related abnormal / long QT[5]	5	1.9	1	2.1	0	0	20	3.2	4	2.2	0	0
--> Thereof causality not assessable (no ECG while exposed to DDI)	0	0.0	1	2.1	0	0	10	1.6	1	0.6	0	0
--> Thereof suspected drug related abnormal QT	4	1.5	0	0	2	3.1	6	0.9	1	0.6	0	0
--> Thereof WHO / CIOMS causality 'possible' for DDI regarding TdP	3	1.2	0	0	0	0.0	3	0.5	1	0.6	0	0
--> Thereof inadequate QT monitoring: no current / pretreatment ECG available[2]	131	50.6	21	43.8	44	67.7	298	47.2	88	48.9	25	48.1
--> Thereof with hypokalemia[3]	22	8.5	3	6.3	8	12.3	54	8.5	17	9.4	5	9.6
--> Thereof with ICD-10 codes predisposing for TdP	52	20.1	6	12.5	14	21.5	72	11.4	19	10.6	6	11.5
--> Thereof with renal insufficiency requiring dose adaptation	20	7.7	1	2.1	na	na	73	11.6	14	7.8	na	na
--> Thereof with supratherapeutic dosing	1	0.4	0	0	na	na	5	0.8	2	1.1	na	na

[1] After exclusion of patients without consent to access original medical records
[2] Current / pretreatment ECG available = ECG performed up to 7 days before co-administration of studied AB with drugs known to cause TdP
[3] K+ < 3.3 mmol/l on day(s) of co-administration
[4] Abnormal QTc = 450 ms for men / 460 ms for women; long QTc = > 500ms
[5] Presence of left bundle branch block / pacing pacemaker / use of amiodarone and (except AB) no other QT prolonging drugs
na = not applicable

Table 12: Adverse events associated with potential medication errors in MQAB users

Case code	*Sex*	*Age*	*Antibiotic(s)*	*Dose Antibiotic*	*Additional QT prolonging drug(s)*	*Dose additional drug(s)*	*Route of admin. AB*	*Route of admin. QT drug*	*Lung transplant*	*QTc*	*K^+*	*Mg^{2+}*	*Heart rate*	*CV diagnoses*
QT1	m	51	Clarithromycin, Azithromycin, Ciprofloxacin	250 mg/3x per week	Domperidon, Ondansetron	30 mg/d, 4 mg/d	p.o.	p.o.	yes	491	3.3	0.98	90	-
QT2	f	67	Clarithromycin	500 mg/d	Domperidone	30 mg/d	p.o.	p.o.	yes	486	4	0.87	68	multiple heart diseases
QT3	m	47	Clarithromycin	1000 mg/d	Ondansetron	8-16 mg/d	i.v.	i.v., p.o.	no	484	4.3	-	55	-
QT4	m	42	Levofloxacin	500 mg/d	Ondansetron	24 mg/d	i.v.	i.v.	no	481	4.3	0.85	81	-
QT5	f	80	Ciprofloxacin	500 mg/d	Citalopram	40 mg/d	p.o.	p.o.	no	513	3.3	0.66	90	-
QT6	m	78	Ciprofloxacin	800 mg/d	Dipiperon, Haloperidol (fix)	120 mg/d, 2 mg/d	i.v.	p.o.	no	518	-	1	61	multiple heart diseases
QT7	f	68	Ciprofloxacin, Azithromycin	250 mg/3x per week	Ciprofloxacin, Domperidon, Citalopram	500 mg/d, 30 mg/d, 10 mg/d	p.o.	p.o.	yes	478			78	cardiomypathy
IA1	f	68	Ciprofloxacin	800 mg/d	na	7 mg/d	i.v.	na	no	na	na	na	na	na
IA2	f	59	Ciprofloxacin	500 mg /d	na	4 mg/d	p.o.	na	no	na	na	na	na	na
IA3	m	71	Ciprofloxacin	800 mg/d	na	2 mg/d	i.v.	na	no	na	na	na	na	na

Pharmacokinetic interactions of MQAB with simvastatin, atorvastatin and tizanidine
Among the 546 individual patients taking clarithromycin or erythromycin we detected 9 patients with co-administration of simvastatin, 6 thereof taking 40 - 80 mg daily. An additional 22 patients were exposed to concomitant use of ≥40 mg atorvastatin daily. In none of these patients symptoms or signs of myopathy including elevated creatine kinase measurements indicated causally related adverse events.
Among the 2247 administered courses of ciprofloxacin we detected 13 with concomitant exposure to tizanidine, 5 thereof with ≥6mg/d. Three patients experienced episodes of hypotension shortly after this combination was administered, and 2 patients were treated with cardiac stimulants (etilefrine and midodrin), but without cessation of tizanidine-ciprofloxacin co-administration (**Table 12**). Causality for the decreases in blood pressure assessment in relation to the DDI was assessed as 'possible' in all three cases.

3.5.7. Conclusion

This study describes the use, co-medication and risk management of MQAB in the real-life setting of a tertiary care hospital with regard to TdP and to selected clinically relevant pharmacokinetic DDI. With the exception of ciprofloxacin, the studied potentially QT-prolonging MQAB were only used in a small proportion of patients. And ciprofloxacin is generally considered 'less torsadogenic' than other quinolones and was only recently added to the list of drugs with a known risk for TdP.[125,147,148] At the same time, it is remarkable how many MQAB users had additional risk factors for TdP. Most notably, more than one third were exposed to additional QT-prolonging drugs, and about one in six MQAB users also had hypokalemia, a risk factor that is usually easy to correct in hospitalized patients.[134,149] Indeed, the SPC of clarithromycin features hypokalemia as an explicit contraindication to its use,[145,150] yet we detected 361 patient-days in which clarithromycin was administered despite current serum potassium below 3.3 mmol/l, representing 8.5 % of all patient-days with exposure to clarithromycin. Renal impairment is another important risk factor for TdP, which may be explained by the reduced renal elimination of many drugs known to cause TdP and an increased risk for electrolyte disturbances.[134] We identified lack of dose-adjustment for renally eliminated MQAB. Although this concerned only a little less than 5% of MQAB users it represents a risk that can be avoided if physicians are aware of it at the time of prescription.
ECGs for the monitoring of abnormal or long QT intervals were available in about 50% in MQAB users with additional QT-prolonging co-medication. The higher

proportion of patients with diagnosed heart diseases among the patients with adequate ECG monitoring may most likely be explained by confounding from the cardiac disease itself rather than a higher awareness for the drug-induced risk of TdP. A high proportion of patients without adequate ECG monitoring had at least one additional risk factors for TdP, and it is likely that additional cases of abnormal / long ECG remained undetected. On the other hand, medical records were searched for adverse events also in patients without ECG-monitoring, and overall only 7 cases of prolonged QTc between 478 and 518 ms were identified, and no case of TdP. The resources required for more intense and guideline-compliant ECG-monitoring must therefore be weighted against expected benefits. Some US tertiary care hospitals have successfully developed and introduced automated algorithms with subsequent alerts for ECG with QTc of >500 ms.[151-154] However, in order for such a system to be effective, a current plus a recent pre-treatment ECG are needed, and also pre-treatment ECGs must be justified.[155,156] Our findings suggest that automated algorithms to improve the risk-assessment may include the following modifiable risk factors: hypokalemia, lack of dose adaptation to renal insufficiency, and ideally also suggestions for alternative co-medication. Nevertheless, the development of cost-effective ECG-monitoring algorithms and their implementation remains challenging, for MQAB users as well as for other high risk groups such as users of psychiatric drugs.[157]

In comparison to QT-prolonging combinations, management implications of our findings regarding selected contraindicated combinations of MQAB with known pharmacokinetic interactions are straightforward. A high proportion of patients with such combinations had associated adverse events, and review of individual situations in original medical record showed that these combinations could have been avoided, as there would have been alternative management options in all cases. Rather simple automated simple alert-algorithms would therefore be an efficient preventive measure with a favorable relation of costs vs. benefits.

In conclusion our study found a considerable number of MQAB users with additional QT-prolonging co-medication and other risk factors for TdP in hospitalized patients, and a high proportion of those had no ECG monitoring. However, adverse events were rarely found, and benefits of intense ECG monitoring as well as benefits of QT-prolonging co-medication in MQAB users have to be weighted against costs. In contrast, correctable co-factors in MQAB users such as hypokalemia, lack of dose-adjustment in renal impairment and selected contraindicated pharmacokinetic interactions are clear targets for implementation as preventive automated alerts in electronic prescribing systems.

3.6. Acetaminophen Overdosing in a Tertiary Care Hospital: Implementation and Outcome Analysis of an Automated Preventive Alert Program

3.6.1. Authors

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3.6.2. Remarks

Significance for thesis & notable feature

This study represents another milestone for this thesis and proof of concept for the overall concept of Interventional Pharmacoepidemiology. The evidence from overdosing that occurred from 2011 to 2013 provided the rationale for the development of a pragmatic, yet highly efficient and effective alert algorithm. The IT department of the University Hospital Zurich provided a timely on-demand extraction of raw-data that was subsequently combined with an alert algorithm that identified patients at risk of clinically relevant overdosing. The challenge of efficiently distinguishing the frequent but purely formal overdosing from prescriptions that needed to be changed was overcome by determining a rational threshold for clinical relevance.

Contributions of the author of this thesis

David Niedrig contributed to the study design, algorithm development and programming, data compilation and interpretation, and wrote the first version of the manuscript.

Publication

This Study has been published as a conference abstract in: Pharmacoepidemiology and Drug Safety 2015; 24: 58-59 and has been submitted as original research for publication to Drug Safety and is currently in the review process.

3.6.3. Background

Acetaminophen has analgesic and antipyretic properties and is one of the most frequently used drugs worldwide. If administered within labeled doses of no more than 4 g per day severe adverse effects are very rare, but if recommended doses are exceeded it is also an intrinsic hepatotoxin.[158] Toxicity is enhanced in patients with cachexia or alcoholism and with repeated overdosing.[87,159] Because of its over-the-counter availability and frequent use intentional and unintentional acetaminophen overdosing frequently occurs in clinical practice, and acetaminophen-induced liver failure is indeed the leading cause of liver transplantations in the US.[158,160] Zhou and colleagues recently investigated the frequency of unintentional acetaminophen overdosing in a tertiary care hospital and reported that 6.6% of acetaminophen users exceeded the recommended maximum dose of 4 g per day.[161] Civan et al. performed a similar analysis and reported overdosing in 2.6%.[162]

In hospitals that use clinical information systems (CIS) with computerized physician order entry (CPOE) all prescriptions are electronically documented, and integrated clinical decision support systems (CDSS) may in theory detect and prevent many medication errors including acetaminophen overdosing.[24,163] However, in clinical practice automated alerts from CDSS are mostly oversensitive and clinically irrelevant.[27,39] Such over-alerting without clinical implications may lead to alert fatigue and ultimately to indiscriminate alert overriding or deactivation of the CDSS.[35] For an effective prevention of acetaminophen overdosing, alerts should therefore only be issued in clinically relevant situations, i.e. when they imply a high risk of adverse events and require the prescriber to take action.[26]

3.6.4. Objectives

Therefore the present study aimed to quantify clinically relevant acetaminophen overdosing and to develop, implement and evaluate the outcome of a highly specific preventive alert algorithm.

3.6.5. Methods

We analyzed acetaminophen overdosing occurring in a Swiss tertiary care hospital with about 1,000 beds and 40 clinical specialty divisions. For all retrospective analyses of acetaminophen overdosing we used our previously described pharmacoepidemiological database containing information on demographics, laboratory results and electronic drug prescriptions extracted on single patient-level from the hospital's electronic clinical information system (CIS).[111] Of note, the CIS

features not only prescriptions, but also a confirmation for each drug's actual administration including its time. The cantonal ethics committee, the hospital's medical director and the hospital's center for clinical research had approved the extraction of anonymized patient data, setup of a pharmacoepidemiological database and analysis, and the access to patients' original medical records for research purposes. We developed and validated an algorithm for the identification of patients with confirmed acetaminophen administrations of > 4 g per day and compared the time periods from 1 Jan 2011 until 31 Dec 2013 (before implementation of an alert system) vs. 1 Jan to 31 Dec 2014 (after implementation of an alert system). By reviewing comprehensive electronic medical records of patients with ≥ 2 subsequent days of overdosing the following additional information was compiled: number, dose, route of administration and Anatomical Therapeutic Chemical Classification System code (ATC-code) of prescribed and administered acetaminophen containing products, cachexia, alcoholism, laboratory results of alanine amino transaminase (ALT) before and after exposure to overdose and other signs and symptoms of acetaminophen-induced liver injury.

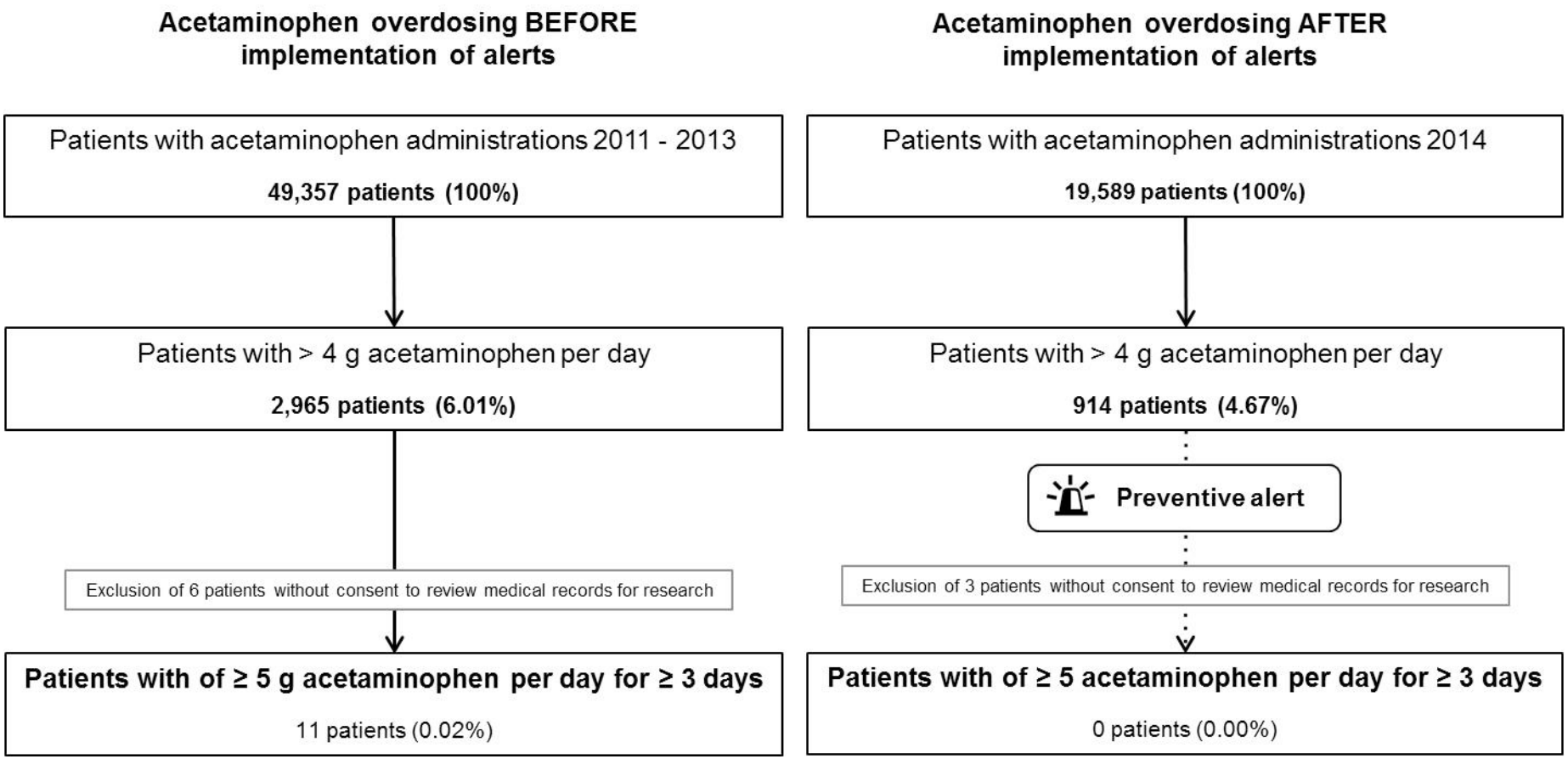
For the effective prevention of acetaminophen overdosing we developed an algorithm within the hospitals CIS that identified patients at risk of repeated clinically relevant acetaminophen overdosing. The algorithm was implemented in 2014 and allowed local safety experts at the Department of Clinical Pharmacology an automated identification of patients with administrations of > 4 g acetaminophen per day. These patients were then validated through review of their electronic medical records. Based on the results from retrospective analyses and currently available literature we classified overdoses of ≥ 5 g per day for ≥ 3 subsequent days as a rational threshold for clinical relevance, i.e. clinicians should take action *before* patients are exposed to such an overdose. For patients suffering from cachexia or alcoholism a lower threshold was chosen, their prescribers were alerted immediately after any administration of ≥ 5 g / day. If our expert review confirmed clinical relevance we notified prescribing physicians through internal mail and if appropriate also through personal phone calls. Subsequent changes to acetaminophen prescriptions were also documented.

3.6.6. Results

Study design and principal results are presented in **Figure 11**. For the time period of 2011 to 2013, i.e. before implementation of the preventive alert system we identified 49,357 individual patients with at least one acetaminophen administration during

hospitalization. Among all acetaminophen users 2,965 patients (6.01 %) were exposed to at least one day with administration of > 4 g acetaminophen per day. Repeated overdosing with ≥ 5 g for ≥ 2 consecutive days occurred in 38 patients, and among these 4 suffered from cachexia and 2 had a documented current history of alcoholism. Clinically relevant overdosing with administrations of 5 to 8 g acetaminophen per day for up to 5 consecutive days had occurred in 11 patients. Alanine aminotransferase (ALT) values before and after exposure to clinically relevant overdosing were available for 9 of those patients. In one patient ALT after overdosing exceeded three times the upper limit of normal. In this case, clinicians suspected acetaminophen as a cause and stopped its administration after exposing this cachectic patient to 5 g acetaminophen for three consecutive days.
In 2014 our proactive alert system was implemented and 19,589 individual patients received at least one acetaminophen administration during hospitalization. 914 (4.67%) thereof were exposed to at least one day with administration of > 4 g per day. The automated screening algorithm of our alert system identified on average about 3 patients per day that were exposed to more than 4 g of acetaminophen per day. These were subject to timely expert review at the early morning of the following day. The assessment whether repeated relevant overdosing was likely took usually less than 5 minutes per patient. Alerts with recommendations to change current acetaminophen prescriptions were issued for 23 patients during one year. In 21 of these cases (91.3%) prescribing physicians were compliant with our recommendations and changed acetaminophen prescriptions accordingly on the same day as the alert was issued. An additional 8 alerts were issued for patients with presence of cachexia or alcoholism for which a maximum dose of 3 g per day was recommended. In 6 of those cases prescription were adapted accordingly. Following the implementation of proactive alerts clinically relevant acetaminophen overdosing of ≥ 5 g per day for more than two days did not occur anymore in 2014.

Figure 11: Acetaminophen overdosing in 2011 - 2013 vs. 2014



3.6.7. Conclusion

Acetaminophen overdosing is a ubiquitous and frequent medication error. In fact the proportion of patients that were exposed to more than 4 g acetaminophen during their hospitalization was 6.0% in our setting and therefore almost identical to the number reported by Zhou et al. in a similar setting in the US.[161] However, a single day with administration of only little more than 4 g acetaminophen, although a formal medication error, is usually clinically irrelevant. In order to avoid alert fatigue proactive preventive safety systems therefore have to find a rational alerting threshold for medication errors that are likely relevant and require prescription changes. Indeed, our further analyses confirmed that the vast majority of acetaminophen overdosing is not repeated and during three years we did not identify a single case of severe acetaminophen-induced liver injury. Typically, overdosing occurs only once per patient and is caused by early administration of a dose actually scheduled for the next day or overlapping administrations when the route of administration was changed from oral- to i.v. or vice versa. Another typical at risk scenario occurs when multiple acetaminophen-containing drugs are prescribed concomitantly, or when there are fixed-dose plus on-demand prescriptions of acetaminophen. On the other hand unintentional iatrogenic acetaminophen hepatotoxicity and even liver failure has been described and justifies preventive measures.[158] Because of the extreme rarity of such tragic events preventive measures must be highly efficient and hence automated, but at the same time they must also be highly specific in order to assure physicians' compliance with alerts. We therefore chose a pragmatic solution for our preventive system, i.e. automated highly sensitive screening was followed by highly specific expert evaluations. Our experience with this system shows that once installed the necessary resources for expert review of prescribed overdose are minimal and that there was a complete absence of clinically relevant acetaminophen overdosing after implementation of our safety system in 2014.

Although we cannot formally prove that our program was the exclusive cause for this absence, it is striking that in the three years before we identified 11 patients with ≥5g acetaminophen per day for ≥3 consecutive days. Furthermore, such a program may have a lighthouse effect regarding a proactive open drug safety culture in a hospital and can serve as a proof-of-concept not only against acetaminophen overdosing but also for the prevention of other suitable relevant medication errors. Such locally customized semi-automated safety programs can be implemented in clinical routine of any hospital with a CIS and dedicated IT specialists and clinical safety experts.

3.7. Development, Implementation and Outcome Analysis of Semi-Automated Alerts for Metformin Dose-Adjustment in Hospitalized Patients with Renal Impairment

3.7.1. Authors

David F. Niedrig, Regina Krattinger, Annika Jödicke, Carmen Gött, Guido Bucklar, Stefan Russmann

3.7.2. Remarks

Significance for thesis & notable features

This study was already initiated in 2012 (i.e. even before the development of alerts against overdosing described above) by Stefan Russmann and supported by Regina Krattinger and the IT department of the University Hospital of Zurich. As of February 2013 David Niedrig managed the alerts in clinical practice. It provided the first local proof of concept that combining a highly sensitive screening for potential ME combined with a highly specific assessment by dedicated drug safety specialists can successfully prevent clinically relevant ME without causing alert fatigue.

Contributions of the author of this thesis

David Niedrig contributed to programming the analyses of data from 2011 and 2012 and contributed to data collection, analysis and interpretation of the data from 2013 to 2015, and wrote the first version of the manuscript.

Publication

This Study was presented as oral presentation and abstract in 2015 at the International Conference of Pharmacoepidemiology (ICPE) in Boston, MA, USA. It was also presented as a poster and abstract at the Congress of the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) 2015 in Zurich.

It is published as a congress abstract in: Pharmacoepidemiology and Drug Safety 2015; 24: 230 and has been submitted as original research to Pharmacoepidemiology and Drug Safety and is currently in the review process under consideration for publication in.

3.7.3. Background

Metformin is primarily used as first line treatment for type 2 diabetes and the most frequently prescribed oral antidiabetic drug worldwide. Its efficacy and tolerability are well established.[164] Because metformin is not metabolized but eliminated unchanged via the kidneys, it can accumulate in impaired renal function. These patients may develop metformin associated lactic acidosis (MALA), a severe adverse drug event with reported fatality rates of 25 - 50 %.[165] Quantification of this risk is challenging and its relevance in clinical practice is subject of ongoing debates.[166] The SPC of metformin states contraindications regarding its use in patients at an increased risk for lactic acidosis, e.g. alcoholics, severe infections, patients suffering from decompensated heart failure or severe impaired renal function with a glomerular filtration rate (GFR) below 30 ml/min. Since 2015, regulatory authorities in Switzerland and the EU allow the use of metformin in patients with mild to moderately impaired renal function if its dose is adapted accordingly and the GFR is regularly monitored, which is in line with many expert recommendations and common clinical practice.[87,167]

Patients in a tertiary care hospital have a high prevalence and incidence of impaired renal function as well as further risk factors for MALA including comorbidities and administration of intravenous contrast agents. Failure to adapt metformin dosing in response to impaired renal function is a preventable medication error. If hospitals use electronic clinical information systems (CIS) data on patients' metformin prescriptions and renal function are documented in a structured electronic format. This information can be linked and used for the automated systematic prevention of MALA. A proactive safety system must be efficient, effective and avoid overalerting. Recommendations to prescribers must therefore not only be highly sensitive, but also highly specific because clinically irrelevant alerts will not be accepted and may lead to alert fatigue and indiscriminate alert overriding.[26]

3.7.4. Objectives

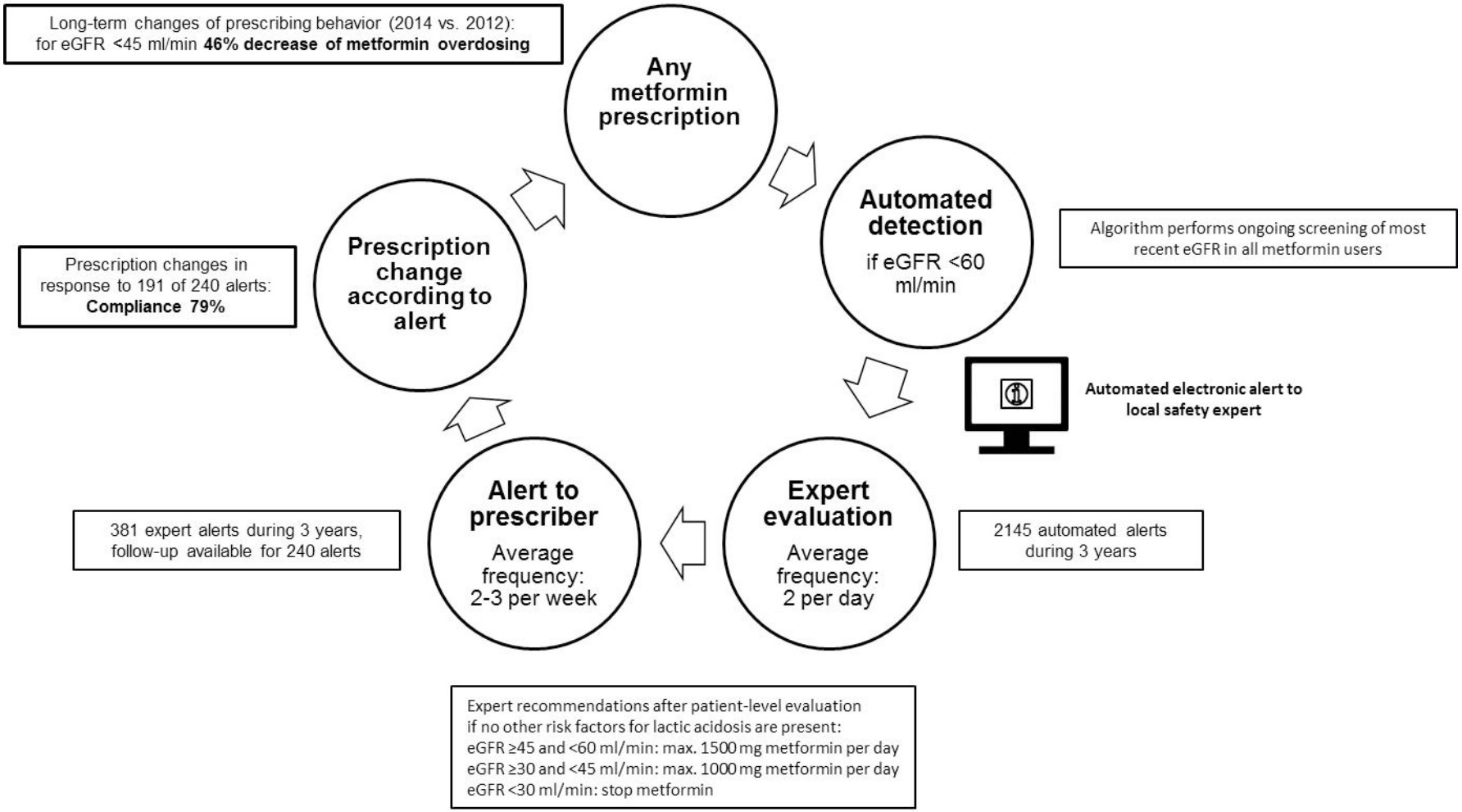
Therefore the present study's aim was the development, implementation and outcome analysis of a highly sensitive and specific automated alert for the prevention of metformin overdosing in hospitalized patients with impaired renal function.

3.7.5. Methods

This proactive medication safety project was performed in a tertiary care hospital that provides medical care to a population of about 1.5 million people and has

approximately 1000 beds and 40 clinical specialty divisions. It features a clinical information system (CIS) by Cistec AG with integrated laboratory data, computerized physician order entry (CPOE) and comprehensive electronic medical records.[168]
We designed and implemented a sensitive automated algorithm that detected any metformin prescription entered through the hospital's computerized physician order entry (CPOE), and for all metformin users the latest available estimated glomerular filtration rate according to the CKD-EPI formula (eGFR) was checked daily. If the eGFR in current metformin users was below 60 ml/min, an automated alert was immediately sent via the CIS's internal email-system to clinical safety experts (SR, a clinical pharmacologist; DN and RK, clinical pharmacists). In a second step these highly sensitive alerts were then subject to a highly specific expert evaluation regarding their clinical relevance. For that purpose patients' original medical records were reviewed not only for the latest prescribed daily metformin dose, but also for unstructured information including causes and circumstances of decreased eGFR, medical diagnoses and further risk factors for MALA. If the current metformin dose exceeded expert consensus, i.e. in-house recommendations supported by published guidelines,[167] a personal alert with metformin dosing recommendations was issued to the prescribers via internal email and if deemed necessary also via telephone. The overall project design is presented as a closed-loop quality control system in **Figure 12**. The project was first initiated in 2011 and is fully operational in its current form since 2012. For the years 2012 to 2014 we also retrospectively analyzed patients for whom an alert had been forwarded to the prescribers in order to evaluate the system's acceptance by the prescribing physicians. The cantonal ethics committee, the hospital's medical director and the hospital's center for clinical research had approved the data extraction, the setup and analysis of the database and the access to original medical records for research purposes.

Figure 12: Study flowchart of semi-automated alerts



3.7.6. Results

During three years since its implementation, the initial highly sensitive screening algorithm generated 2145 automated alerts to the local safety experts, i.e. approximately 2 per day. The subsequent daily evaluation of the alerts including review of the respective patients' electronic medical records required approximately 2 to 10 minutes per patient. Following this highly specific expert evaluation that included also non-structured medical information changes of metformin therapy were recommended for 381 cases (17.8 %), i.e. approximately 2 to 3 per week (**Table 13**). In order to evaluate the outcome of the system we also analyzed follow-up data, which was available for 240 patients. Among those, metformin dose had been reduced or stopped in 191 patients, corresponding to a compliance of 79 % with our recommendations. In case of non-compliance we found that there were typically only mild discrepancies between recommended and administered doses, e.g. 1700 instead of 1500 mg metformin per day.

In addition we were also able to search our local clinical records and databases for cases of MALA. From 2011 to 2014 we identified 8 cases of MALA in patients with renal impairment. They had all occurred in circumstances where no timely recommendation could have been generated, such as metformin overdosing before hospital admission. In all MALA cases we identified also other contributory and triggering causes and risk factors for lactic acidosis. While the overall number of alerts issued to the prescribers remained constant during three years, the number of any metformin prescription in patients with an eGFR < 45 ml/min and the number of patients with pronounced metformin overdosing declined from 2012 to 2014 (**Table 13**).

Table 13: Metformin prescriptions in patients with eGFR < 60 ml/min and subsequently issued alerts

Year	*Automated alerts to safety experts*	*Expert alerts to prescribers*	*Patients with available follow-up*	*Sex m / f*	*Mean age*	*eGFR 31 - 44 ml/min at time of alert*	*eGFR < 30 ml/min at time of alert*	*Overdose ≥ 1000 mg compared to recommended dose at time of alert*	*Compliance n*	*%*
2012	643	135	90	57 / 33	73	41	16	52	81	90.0
2013	693	123	88	51 / 37	72	30	13	36	67	76.1
2014	809	123	62	40 / 22	74	19	7	24	43	69.4

3.7.7. Conclusion

There is an ongoing debate regarding the causal role of metformin in cases of lactic acidosis, and we realize that metformin overdosing is rather a contributory cause in patients with other acute conditions associated with hypoxia, than a single sufficient cause. However, regardless of the interaction of several contributing causes, there is no doubt that metformin aggravates any lactic acidosis, that its dose must be at least reduced in moderate to severe renal impairment, and that particularly in patients with several risk factors for lactic acidosis metformin must be stopped. The observed cases of MALA, some with metformin doses clearly exceeding current recommendations, underline that the issued alerts address a clinically relevant adverse drug event.

The presented proactive drug safety project against metformin overdosing in impaired renal function applied an innovative 2-step approach, hence called “semi-automated”. First, a highly sensitive fully automated screening algorithm identified any current metformin users with an eGFR below 60 ml/min. It is important to note that this ongoing daily screening algorithm also detects patients with a normal eGFR at the time of the first in-hospital metformin prescription when the eGFR later decreases below this threshold during hospitalization. In a second step local clinical safety experts performed a highly specific expert review that is difficult to automate because also unstructured medical information and the latest specific situation of individual patients have to be considered. However, the initial screening was a necessary prerequisite in order to increase the system’s efficiency. Even with limited resources, i.e. approximately 5 minutes per patient, it was then possible to evaluate on average two patients per day that the screening algorithm had detected. The compliance of 79% indicates that such a combined system can provide a solution for a major challenge that current clinical decision support systems face. For most potential medication errors only the additional consideration of unstructured medical information and clinical expertise can increase the specificity of an alert to a level that does not cause alert fatigue and non-compliance of prescribing physicians. Therefore the current project is also an important proof-of-concept for an approach that can reach high efficiency and efficacy in clinical practice and is yet easy to implement with limited resources. Furthermore, the decrease regarding metformin overdosing in the most vulnerable patients with an eGFR < 45 ml/min suggests that such a system may also have an educative effect and thereby contribute to an increased awareness of local prescribing physician

4. Conclusions and Outlook

4.1. Preventing Medication Errors in the Past

Before the advent of CPOE and CDSS, the identification of ME relied on manual chart review and individual assessment of a patient's prescriptions. Systematic analyses of medical records revealed that many ME were related to transcription errors or incomplete or misleading prescriptions. Additionally, knowledge about potentially critical ME such as pharmacokinetic DDI or dose adaptations in patients with renal impairment was not readily available upon prescription or administration of drugs. In clinical practice, local specialists, e.g. clinical pharmacologists or pharmacists, aimed to prevent ME by contacting the prescribers after detecting a potentially problematic medication during ward rounds or upon dispensing of the drugs. While the introduction of CPOE clearly improved drug safety in hospital clinical practice by reducing certain ME, CDSS did not fulfill the initially high expectation regarding improvements to pharmacotherapy. These systems typically focused on DDI and produced too many highly sensitive but non-specific alerts that were deemed mostly irrelevant for the management of individual patients. Lately, drug safety and the prevention of avoidable ADE in hospitals became increasingly important topics and incentives were announced in order to promote the implementation of CPOE and CDSS.

4.2. Preventing Medication Errors Today

Currently approximately 50 % of the Swiss hospitals use CPOE with various degrees of CDSS implementation. The lack of standardization regarding CDSS and their knowledge databases as well as the wide variety of CIS and CPOE are considerable challenges for the development, implementation and validation of efficient and effective alerts. Despite considerable efforts to improve CDSS, they are only rarely fully integrated in hospital clinical routine. However, targeted individual evaluations and mass-analyses of hospital drug prescription- and administration data can be performed efficiently if the required data is available in a suitable format and quality. By subsequently validating potential ME in patients' medial records, their frequency and clinical relevance can be systematically assessed. Subsequently, individually developed highly specific alert algorithms can be implemented in hospital clinical routine. Some preventive alerts use timely patient-related data and have been shown to successfully prevent clinically relevant ME. Changes to patients' pharmacotherapy

upon admission and discharge have been identified as a major source of ME. A national eHealth system for an automated and secure transfer of patient data between healthcare providers would be necessary to systematically prevent these and certain other ME, but is not yet available.

4.1. Preventing Medication Errors in the (not too Distant) Future

If computers are to discriminate between potential ME and clinically relevant ME reliably and fully automated, they will often need to assess a multitude of complex, dynamic and occasionally non-structured data. Making computers understand free text or images, such as an ECG readout or a nurses note on a suspected drug-related ADE, is highly challenging. This is however necessary because CDSS need to consider certain risk factors for ME, e.g. crucial differential diagnoses, suspected alcoholism or already manifest signs and symptoms of an ADE. But even reliable structured basic information, e.g. the dose of prescribed or administered drugs, will not be available in many hospitals in the next few years. Considering the moderate progress of the implementation of CPOE / CDSS in Swiss hospitals and the national eHealth infrastructure, more pragmatic and system-independent solutions for the prevention of ME in hospitals are needed - especially for those ME with potentially severe ADE. Increasing healthcare costs and the limited availability of clinical pharmacists and pharmacologists will not allow an intensified manual monitoring for ME and ADE in hospitals. Although their advice is usually well accepted by clinicians and has been shown to significantly improve patient outcomes, it is not possible to comprehensively and constantly monitor all hospitalized patients with their prescribed and administered drugs, lab parameters and current diagnoses.

A more promising strategy might be to pragmatically combine the best of these two worlds: The data formats and infrastructure of CIS and CPOE in hospitals will likely continue to vary considerable. It is therefore unlikely that a standardized interface for CDSS will be established anytime soon. However, this thesis demonstrated that it is possible to build a local pharmacoepidemiological database if an interface with a commercially available CIS is used. Using similar methods as applied in this thesis, the data can then be used by local drug safety specialists for an ongoing analysis and prevention of ME. Identifying the clinical relevance of ME would be performed by using a CDSS software application specifically designed for the semi-automated detection of ME running on data in the most simple conceivable format.
Clinical pharmacists or pharmacologists could use such a CDSS to efficiently assess which patients are at risk of potential ME and which thereof are of clinical relevance. Such local drug safety specialists could act as gatekeeper for alerts to the prescribers. The CDSS would support this process by facilitating benefit risk assessments, providing default management recommendations and document issued (and withheld) alerts. Thereby prescribers would only be alerted if a local drug safety specialist deemed a ME as clinically relevant and would be contacted by a known hospital staff member that has already reviews the patient in the CIS.

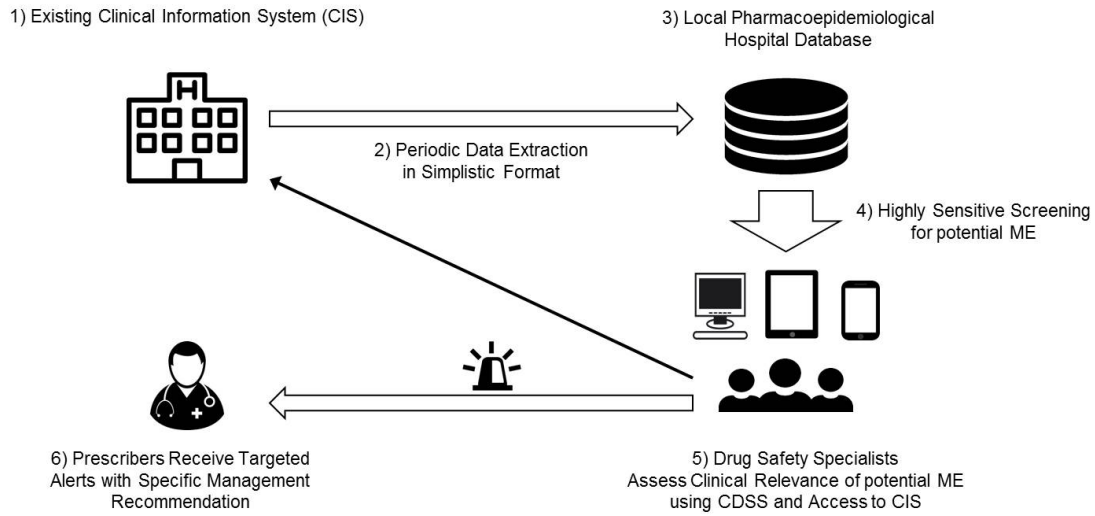


Figure 13: Concept for Drug Safety Management in Hospitals by Local Experts Through Semi-automated Alert Algorithms, concept adapted from: Drug Safety Manager - Development of an Integrated Concept and Application for Drug Safety Analyses, Interventions and Outcomes Research in Hospitals presented by Stefan Russmann and David Niedrig at the International Congress of Pharmacoepidemiology 2015 in Boston, MA, USA and at the Swiss ISoP Chapter Meeting in Zurich 2014.

Pooling and comparing different local hospital pharmacoepidemiological databases and their daily routine of assessing and preventing potential ME would also support benchmarking of hospitals' drug safety. The knowledge database of the CDSS could be constantly improved by crowed-sourced feedback and best practice sharing. Finally, combining such datasets would also allow a highly efficient signal detection of other potential safety issues for automated pharmacovigilance signal generation.

Combining the high sensitivity of computers and their ability to handle an almost unlimited amount of structured data with the human ability to understand the specific clinical context of a potential ME is likely the key to a paradigm shift in hospital drug safety that has the potential to significantly improve patients' pharmacotherapy in clinical practice.

5. Acknowledgements

5.1. Potential Conflicts of Interests

These studies were supported by unrestricted research grants to Stefan Russmann from the Swiss National Science Foundation, ID Suisse AG and Takeda Pharma AG. David Niedrig worked as consultants for Takeda Pharma AG, but without relation to this thesis or the within presented studies.

5.2. Thank you!

Eva Alther Niedrig, my family and friends
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For inviting me to the ISoP meeting in 2012 in Zurich where everything started, setting up of the studies and getting funding, accepting- and trusting me as his Padawan, teaching and discussing concepts of drug safety and pharmacoepidemiology, supporting and revising the writing of the manuscripts and the thesis and being part of the doctoral committee of the doctoral examination.

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Guido Bucklar and Michael Fetzer from the IT departement of the USZ
For providing the raw data and programming and implementing the paracetamol and metformin alerts into the hospitals clinical information system.

6. Statement of Originality

Concerning the present thesis with my signature I confirm:

• that I have written and composed it independently,

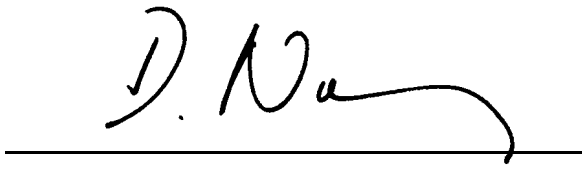
• that I have not submitted it to any other university,

• that I have documented all methods, data and processes truthfully,

• that I have not manipulated any data,

• that I have mentioned all persons who were significant facilitators of the work, and

• that I have not committed any of the forms of plagiarism described in the „Citation etiquette“.



7. Scientific Publications and Presentations

Published original research as first author

- Second-generation antipsychotics in a tertiary care hospital: prescribing patterns, metabolic profiles, and drug interactions.
  Authors: David F. Niedrig, Carmen Gött, Anja Fischer, Sabrina T. Müller, Waldemar Greil, Guido Bucklar, Stefan Russmann
  Published in: International Clinical Psychopharmacology: January 2016; 31(1): 42-50.

Original research as first author, accepted for publication

- Drug Safety of Macrolide and Quinolone Antibiotics in a Tertiary Care Hospital: Administration of Interacting Comedication and QT-Prolongation.
  Authors: David F. Niedrig, Sarah Mächler, Liesa Hoppe, Natascia Corti, Helen Kovari, Stefan Russmann
  Accepted for publication March 2016 in: European Journal of Clinical Pharmacology

Published conference abstracts as first author

- Acetaminophen Overdosing in Hospitalized Patients: Retrospective Analysis and Implementation of Preventive Semi-automated Alerts
  Authors: David F. Niedrig, Guido Bucklar, Michael Fetzer, Sarah Mächler, Carmen Gött, Stefan Russmann
  Published as a conference abstract in: Pharmacoepidemiology and Drug Safety 2015; 24: 58-59.

- Retrospective Mass-Analysis of Hospital Prescription Data for Medication Errors and Subsequent Development of Highly Specific Alert Algorithms with ID PHARMA CHECK®
  Authors: David F. Niedrig, Andre Sander, Daniel Diekmann, Stefan Russmann
  Published as a conference abstract in: Pharmacoepidemiology and Drug Safety 2015; 24: 65-66.

- Development, Implementation and Outcome Analysis of Semi-Automated Alerts for Metformin Dose-Adjustment in Hospitalized Patients with Renal Impairment
  Authors: David F. Niedrig, Regina Krattinger, Annika Jödicke, Carmen Gött, Guido Bucklar, Stefan Russmann
  Published as a conference abstract in: Pharmacoepidemiology and Drug Safety 2015; 24: 230.

Published original research as co-author

- Rivaroxaban postmarketing risk of liver injury
  Authors: Stefan Russmann, David F. Niedrig, Mathias Budmiger, Caroline Schmidt, Bruno Stieger, Sandra Hürlimann, Gerd A. Kullak-Ublick
  Published in: Journal of Hepatology 2014; 61: 293-300.

- Allergy-like immediate reactions during the use of herbal remedies as reported in VigiBase®
  Published online in March 2016 in: Drug Safety.
  DOI 10.1007/s40264-016-0401-5

Published conference abstracts as co- author

- Drug Safety Manager - Development of an IntegratedConcept and Application for Drug Safety Analyses, Interventions and Outcomes Research in Hospitals
  Stefan Russmann, David F. Niedrig, Gyorgy Olah, Luzi Zappa
  Published as a conference abstract in: Pharmacoepidemiology and Drug Safety 2015; 24: 64-65.

Oral conference presentations

- *European and Swiss Congress of Internal Medicine ESCIM 2014, Geneva:*
  Acetaminophen Overdosing in Hospitalized Patients: Retrospective Analysis and Implementation of Preventive Semi-automated Alerts

- *Swiss Chapter Meeting of the International Society of Pharmacovigilance IsoP 2015, Zurich:*
  Drug Safety Manager - Development of an Integrated Concept and Application for Drug Safety Analyses, Interventions and Outcomes Research in Hospitals

- *International Congress of Pharmacoepidemiology and Therapeutic Risk Management ICPE 2015 Boston MA:*
  Development, Implementation and Outcome Analysis of Semi-Automated Alerts for Metformin Dose-Adjustment in Hospitalized Patients with Renal Impairment

- *Jahreskongress der Gesellschaft der Schweizerischen Amts- und Spitalapotheker GSASA 2015, Zurich:*
  Retrospective Mass-Analysis of Hospital Prescription Data for Medication Errors and Subsequent Development of Highly Specific Alert Algorithms with ID PHARMA CHECK®

Awards

- University Hospital Zurich (USZ) Quality Award 2014 for: Acetaminophen Overdosing in Hospitalized Patients: Retrospective Analysis and Implementation of Preventive Semi-automated Alerts

- Annual Meeting 2015 of the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA), award for best oral presentation for: Retrospective Mass-Analysis of Hospital Prescription Data for Medication Errors and Subsequent Development of Highly Specific Alert Algorithms with ID PHARMA CHECK®

8. Appendix

8.1. Rivaroxaban postmarketing risk of liver injury

8.1.1. Authors

Stefan Russmann, David F. Niedrig, Mathias Budmiger, Caroline Schmidt, Bruno Stieger, Sandra Hürlimann, Gerd A. Kullak-Ublick

8.1.2. Remarks

Significance for thesis & notable feature

While this study is not directly related to the prevention of ME in hospitalized patients it nevertheless contributes to raise awareness of potential risks associated with a commonly used new drug. It is a good example for the fast analysis of several very large international pharmacovigilance databases in response to a new safety signal. Later, signs and symptoms of ADE, i.e. increased liver parameters and jaundice could be used to trigger semi-automated alerts that notify local drug-safety experts to a potentially drug-related adverse event. Algorithms for such alerts could specifically include drugs that currently require careful monitoring of exposed patients in order to issue timely recommendations.

Contributions of the author of this thesis

David Niedrig contributed to the CIOMS case assessment and contributed to FAERS data acquirement, management and analyses with specifically developed algorithms, overall data interpretation, and revisions of the manuscript.

Publication

This study is published as original research in: Journal of Hepatology 2014; 61: 293–300.

8.1.3. Background

Rivaroxaban is an oral direct factor Xa inhibitor that has been marketed worldwide since 2008 for the primary and secondary prevention and treatment of thromboembolic disorders.[169,170] Although liver injury was observed in premarketing trials of rivaroxaban[171], postmarketing cases of liver injury associated with rivaroxaban have not been published so far. Safety issues of newly marketed drugs including drug-induced liver injury (DILI) are typically identified during the first five years after marketing, and spontaneous reporting systems play an important role as a sensitive source of information for the detection of new postmarketing safety signals.

8.1.4. Objectives

We therefore evaluated postmarketing cases of liver injury associated with rivaroxaban reported to our regional pharmacovigilance center and performed search queries in three large international pharmacovigilance databases for comparable cases.

8.1.5. Methods

Report of 14 cases of liver injury associated with rivaroxaban, including two with liver biopsy, and search queries in three large international pharmacovigilance databases for comparable cases.

8.1.6. Results

Case #1

A 78-year-old male patient had total knee replacement for which he received thromboprophylaxis with dalteparin for 10 days and thereafter rivaroxaban (Xarelto®, Bayer HealthCare) 10 mg/d. Approximately 14 days after start of rivaroxaban the patient developed painless jaundice, pruritus, fatigue, nausea and unintentional weight loss of 5 kg. Rivaroxaban was stopped 19 days after start, but it was not until another 10 days later that the patient was rehospitalized with determination of laboratory values. Upon admission alanine aminotransferase (ALT), alkaline phosphatase (AP) and total bilirubin (TB) were increased 2.5, 2.9 and 15.5 times the upper limit of normal (ULN), respectively. Viral serology and autoantibodies were negative. Abdominal ultrasound and computer tomography (CT) showed cholecystolithiasis but no signs of biliary obstruction. A liver biopsy was performed 20

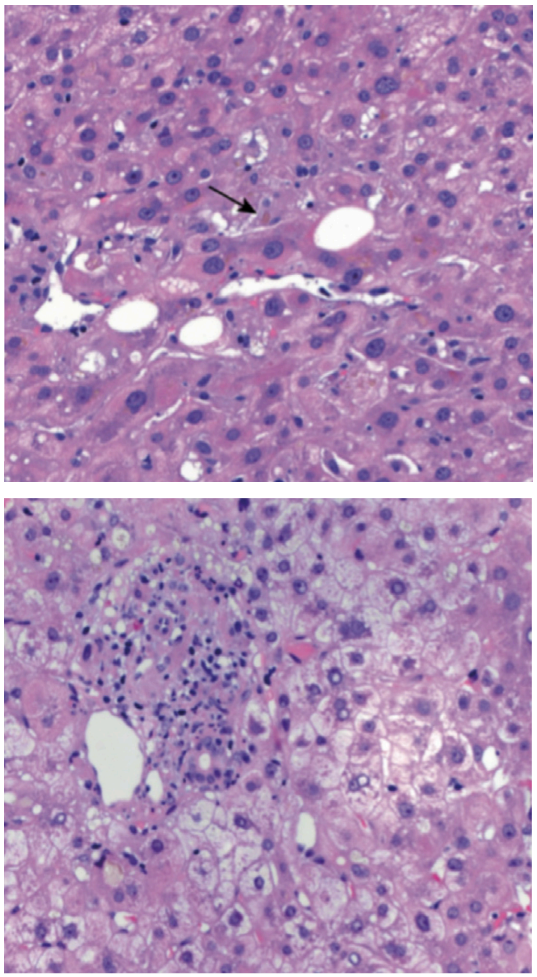
days after discontinuation of rivaroxaban. Histology showed cholestasis and portal inflammation with eosinophilic infiltrates, compatible with drug-induced liver injury (**Figure 14**). Other recently administered drugs were a single i.v. dose of 2g cefazolin before knee replacement and postoperative analgesic treatment with acetaminophen and metamizole (=dipyrone) up to 4 g/day each for 10 days. During the further course the patient eventually developed a paralytic ileus and died 6 weeks after rehospitalization. The findings are also summarized in **Table 14**.

According to standardized RUCAM criteria for the assessment of drug-induced liver injuries [172-174] we assigned a causality of “highly probable” (total score: 9) to rivaroxaban. Key criteria for this assessment were a close and plausible temporal relationship, a known and labeled adverse drug reaction, compatible histological findings, and negative differential diagnosis for alternative causes. Specifically, temporal relationship, only mild ALT increase and histology were not compatible with acetaminophen hepatotoxicity; dalteparin and metamizole had been stopped approximately 14 days, and cefazolin single dose was given 24 days before onset of symptoms. Other drugs were therefore classified as unlikely alternative causes.

Figure 14: Liver histology in cases #1 and #2

Histology in the two patients where needle liver biopsies were performed revealed almost identical morphological findings with more pronounced changes in case #2. Liver parenchyma shows a centrilobular accentuated cholestasis (A, arrow) with prominent Kupffer cells and focal ballooning of periportal hepatocytes (B). There is a mainly portal inflammation of mixed cellularity, focal with many eosinophilic granulocytes and some periductal reinforcement (C, B). Interlobular bile ducts show an alteration of the epithelium with intraepithelial lymphocytes (D and inset, arrow) and some ductular reaction (D, inset, arrowhead). No ductopenia or fibrosis is present. (H&E; inset panel D: cytokeratin 7 immunohistochemistry stain of bile ducts).

Liver histology, case #1



Liver histology, case #2

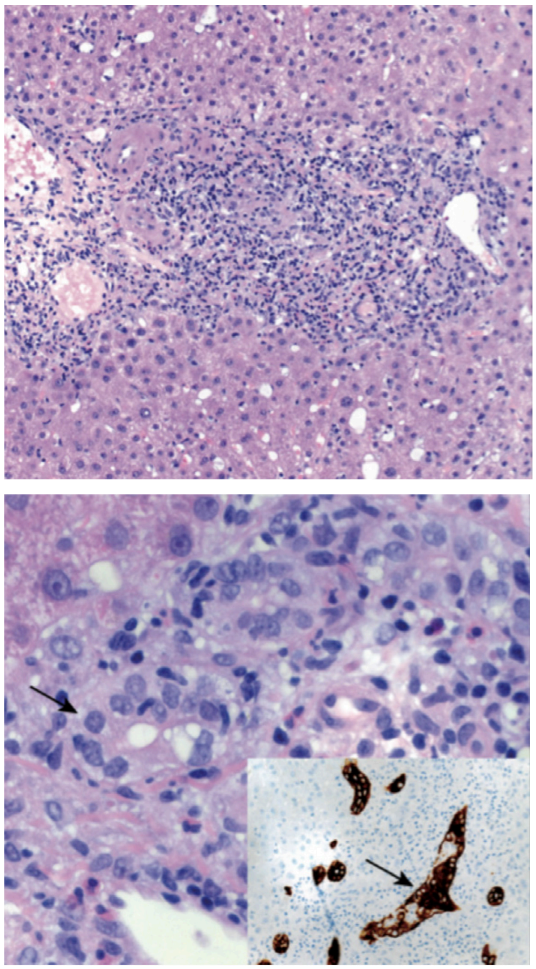


Table 1: Case presentations, continued on next 2 pages

Case #	Age	Sex	RVXB indication	RVXB dose/day (mg)	RVXB treatment duration (days)	Latency time[1] (days)	Symptoms	ALT (xULN)[2] initial max	AP (xULN)[3] initial max	R[4]	TB (xULN)[5] initial max	Outcome	Differential diagnosis	RUCAM[6] causality score	RUCAM[5] causality class	Comments
1	78	m	Knee replacement	20	19	14	Painless jaundice, nausea	2.5 (day30)	2.9 (day 30)	0.8	15.5 (day 30) 21.6 (day 42)	Death (paralytic ileus)	Vira serology for HBV, HCV, CMV, EBV negative; autoantibodies and imaging negative. No other suspicious drugs or events causing liver injury identified.	9	Highly probable	Liver biopsy performed (see Figure)
2	83	f	Knee replacement	10	21	16	Painless jaundice, nausea	7.8 (day20)	6.8 (day20) 7.1 (day 29)	1.2	13.9 (day 20) 17.1 (day 27)	Recovery	Viral serology for HAV, HBV, HCV, CMV, EBV negative; autoantibodies and imaging negative. Diclofenac alternative possible cause.	5	Possible	Liver biopsy performed (see Figure)
3	74	m	Atrial fibrillation	20	51	<50	Painless jaundice	4 (day 51) 5.1 (day 55)	<1 (day 51)	5.1	3.1 (day 51) 3.7 (day 52)	Recovery	Viral serology for HBV negative; IgG and imaging negative. No other suspicious drugs or events causing liver injury identified.	7	Probable	Meets biochemical criteria for Hy's case[7].
4	63	m	Atrial fibrillation	20	6	5	Nausea and vomiting	7.8 (day 7)	<1 (day 6)	7.8	<1 (day 6)	Recovery	Amiodarone 600 mg/d may be alternative or contributory cause. No other events that suggest alternative cause.	3	Possible	Nausea improved immediately after stop of RVXB while high dose amiodarone was continued (no follow-up of ALT available).
5	91	f	Atrial fibrillation	15	34	14	Painless jaundice, nausea	2.5 (day 34)	7.8 (day 37)	0.3	8.4 (day 34)	Recovery	Viral serology for HAV, HBV, HCV, HDV, HEV negative; ANA, ANCA, Anti-MPO, Anti-PR3 negative; imaging negative. No other suspicious drugs or events causing liver injury identified.	9	Highly probable	
6	64	f	Atrial fibrillation	20	40	<40	No symptoms	6.3 (day 40)	1.5 (day 40)	4.1	n.a.	Recovery	No other suspicious drugs or events causing liver injury identified.	7	Probable	

Case #	Age	Sex	RVXB indication	RVXB dose/day (mg)	RVXB treatment duration (days)	Latency time[1] (days)	Symptoms	ALT (xULN)[2] initial max	AP (xULN)[3] initial max	R[4]	TB (xULN)[5] initial max	Outcome	Differential diagnosis	RUCAM[6] causality score	RUCAM[6] causality class	Comments
7	75	m	Knee replacement	20	15	15	Painless jaundice	10.6 (day 18) 11.3 (day 22)	3.2 (day 18) 6.2 (day 33)	3.4	4.5 (day 18) 9.0 (day 22)	Recovery	Imaging negative; HBV, HCV, EBV, CMV, ANA, Anti-dsDNA and IgG negative. No other suspicious drugs or events causing liver injury identified.	9	Highly probable	
8	69	f	Knee arthroscopy	10	10	13	Fatigue, loss of appetite	2.7 (day 12)	<1 (day 26)	2.7	n.a.	Recovery	No differential diagnostic investigations performed, because presentation and history did not suggest alternative causes. No other suspicious drugs or events causing liver injury identified.	9	Highly probable	"Positive rechallenge": Reexposure to RVXB after knee replacement 6 months later with subsequent increase of AP (2.8 xULN) 11 after surgery and restart of RVXB; again recovery after stop.
9	61	f	Knee surgery (cruciate ligament plasty)	10	24	20	Jaundice, nausea, pruritus	13.6 (day 24)	1.5 (day 24)	9.3	3.7 (day 24)	Recovery	HBV vaccinated. Acetaminophen possibly contributory but unlikely primary cause (only 3g/day, jaundice and long latency time not typical for intrinsic acetaminophen hepatotoxicity).	6	Probable	Meets biochemical criteria for Hy's case[7]. Acetaminophen may have contributed to ALT increase.
10	60	f	Knee replacement	10	17	14	Jaundice, fatigue, vomiting,	18.6 (day 17) 19.9 (day 20)	n.a.	n.a.	4.2 (day 17) 8.4 (day 13)	Recovery	Imaging negative; HAV, HBV, HCV, ANA, Anti-SLA/SM/mitochondria negative. No other suspicious drugs or events causing liver injury identified.	6	Probable	Meets biochemical criteria for Hy's case[7]. Acetaminophen may have contributed to ALT increase.
11	41	f	Leg surgery after trimalleolar Fx	10	27	20	Jaundice, nausea and vomiting, pruritus	53.7 (day 27)	3.4 (day 27)	15.6	4.8 (day 30)	Recovery	HAV, HBV, HCV, HEV, CMV, EBV, ANA and Anti-sm negative, IgG normal. Imaging negative. No other suspicious drugs or events causing liver injury identified.	7	Probable	Meets biochemical criteria for Hy's case[7]. Acetaminophen may have contributed to ALT increase.
12	78	f	Knee replacement	10	62	62	Jaundice, nausea, diarrhea	14 (day 62)	2.1 (day 62)	6.5	n.a.	Recovery	Acetaminophen postoperatively not documented but possible. No suggestion for alternative causes but no formal exclusion.	5	Possible	

Case #	Age	Sex	RVXB indication	RVXB dose/day (mg)	RVXB treatment duration (days)	Latency time[1] (days)	Symptoms	ALT (xULN)[2] initial max	AP (xULN)[3] initial max	R[4]	TB (xULN)[5] initial max	Outcome	Differential diagnosis	RUCAM[6] causality score	RUCAM[6] causality class	Comments
13	73	m	Knee replacement	10	3	3	Jaundice, nausea, mild pain	6.1 (day 5)	2.5 (day 5)	2.5	n.a.	Recovery	Imaging negative. No other suspicious drugs or events causing liver injury identified.	6	Probable	Unusually short latency time. Cefazolin preoperative single i.v. application, but cefazolin previously well tolerated.
14	42	f	Leg surgery after Maisonneuve-Fx	10	31	29	Jaundice, nausea	23.5 (day 30)	3.2 (day 30)	7.3	2.8 (day 30) 3.0 (day 54)	Recovery	Viral serology and autoantibodies negative. No other suspicious drugs or events causing liver injury identified.	8	Probable	
Legend Table 1																
[1]	Time from start of RVXB to first symptoms or signs of liver injury.															
[2]	Alanine aminotransferase, expressed as multiples of upper limit of normal. Time in relation to start of RVXB.															
[3]	Alkaline phosphatase, expressed as multiples of upper limit of normal. Time in relation to start of RVXB.															
[4]	Laboratory classification of drug-induced liver injury (see also reference 2), where R = ratio ALT/AP, where both are expressed as multiples of upper limit of normal															
[5]	Total bilirubin, expressed as multiples of upper limit of normal. Time in relation to start of RVXB.															
[6]	Roussel Uclaf Causality Assessment Method, endorsed by the Council of International Organizations of Medical Sciences (see also references 1 and 2).															
[7]	Hy's case criteria: ALT >3x ULN and TB >2x ULN without initial AP increase / cholestatic enzyme pattern (see also reference 6).															

Case #2

An 83-year-old female patient had total knee replacement for which she received thromboprophylaxis with dalteparin for 9 days and thereafter rivaroxaban 10 mg/d. Approximately 13 days after start of rivaroxaban the patient developed painless jaundice, pruritus, fatigue, nausea and unintentional weight loss of 5 kg. Twenty days after start of rivaroxaban the patient was rehospitalized, and another day later rivaroxaban was replaced by dalteparin. Upon admission ALT, AP and TB were increased 7.8, 6.8 and 13.9 times the ULN, respectively (**Table 14**). Viral serology and autoantibodies were negative. Abdominal ultrasound and CT showed cholecystolithiasis but no signs of biliary obstruction. A liver biopsy was performed 5 days after stop of rivaroxaban and was compatible with drug-induced liver injury showing a similar histology (Figure) as in case #1. Other recently administered drugs were a single i.v. dose of 2g cefazolin before knee replacement and analgesic treatment with acetaminophen 4 g/day and diclofenac 150 mg/d for 9 days postoperatively (followed by an on-demand prescription for another 20 days, but unknown actual use), and metamizole 1000 mg and 500 mg on postoperative days 1 and 3, respectively. The patient was treated with cholestyramine and subsequently recovered over the following weeks.

Formal RUCAM assessment classified rivaroxaban‘s causality as “possible” (total score: 5), based on the key criteria of a close and plausible temporal relationship, a known and labeled adverse drug reaction, compatible histological findings and negative differential diagnosis for alternative causes except for diclofenac use. Nevertheless, in contrast to rivaroxaban, fixed-dose diclofenac was stopped 16 days before onset of symptoms, and rivaroxaban therefore remains the most likely cause of liver injury.

Cases #3-14

Over the past 4 years and in our function as a regional pharmacovigilance center we received another 12 reports of liver injury associated with rivaroxaban and an at least possible causal relationship based on RUCAM criteria. In addition to our primary documentation we now performed an extensive reevaluation including formal causality assessment. For that purpose we contacted primary reporters and other treating physicians and hospitals and obtained all available relevant follow-up information. These cases are summarized in **Table 14**, and their detailed RUCAM classifications are presented in **Table 15**.

Table 15: Detailed RUCAM causality assessment and scores for all 14 cases

Case #	1	2	3	4	5	6	7	8	9	10	11	12	13	14
RUCAM criteria														
hepatocell or chol/mix	chol	chol	hepatocell	hepatocell	chol	mix	mix	?	hepatocell	?	hepatocell	hepatocell	mix	hepatocell
1 (temporal relationship)	2	2	2	2	2	2	2	1	2	2	2	2	1	2
2 (course after drug cessation)	2	0	2	0	2	2	1	2	3	2	3	2	2	2
3.1 (risk factors, alcohol)	0	0	0	0	0	0	1	0	0	0	0	0	0	0
3.2 (risk factors, age)	1	1	1	1	1	1	1	1	1	1	0	1	1	0
4 (concomitant drugs)	0	-2	0	-2	0	0	0	-2	-2	-2	-2	-2	0	0
5 (exclusion of non-drug causes)	2	2	0	0	2	0	2	2	0	1	2	0	0	2
6 (labeling / previous information on hepatotoxicity)	2	2	2	2	2	2	2	2	2	2	2	2	2	2
7 (rechallenge)	0	0	0	0	0	0	0	3	0	0	0	0	0	0
TOTAL SCORE	**9**	**5**	**7**	**3**	**9**	**7**	**9**	**9**	**6**	**6**	**7**	**5**	**6**	**8**
Score interpretation	**highly prob.**	**possible**	**probable**	**possible**	**highly prob.**	**probable**	**highly prob.**	**highly prob.**	**probable**	**probable**	**probable**	**possible**	**probable**	**probable**

For detailed description of RUCAM criteria see also references 167 (Aithal et al. 2011) and 168 (Danan and Benichou 1993)

Reports in International Pharmacovigilance Databases

Cases of liver injury associated with rivaroxaban should be reported to pharmacovigilance systems worldwide, and we therefore also performed searches in databases of international postmarketing spontaneous reporting systems. The database of the World Health Organization (WHO UMC VigiBase, access date 2013-11-28) contains, including our own cases, reports of 179 cases that are compatible with DILI (classified under 19 selected hepatobiliary WHO-ART reaction terms) where rivaroxaban was reported as a suspected cause; the database of the European Medicines Agency (EMA EudraVigilance, access date 2013-11-03, data censored 30 September 2013) contains 375 events classified under 21 selected hepatobiliary MedDRA reaction terms where rivaroxaban was a suspected cause; and the database of the US Food and Drug Administration (FDA FAERS, data censored 31 December 2012, extracted in November 2013 by the FDA in response to our request under the Freedom of Information Act) contains 87 cases classified under the 21 selected MedDRA terms. For details on searched terms and reported hepatic events see supplementary material (S.1).

These reports have limitations and must therefore be interpreted with caution: in the absence of detailed information the causal role of rivaroxaban regarding the reported hepatic outcomes remains uncertain; due to unknown reporting rates and population exposure spontaneous reporting systems cannot provide reliable quantitative risk estimates; pharmacovigilance systems may contain duplicate reports, and in our EudraVigilance search several adverse events may refer to only one individual case. Nevertheless, these reports can be interpreted as a signal in support of the hypothesis that our cases may represent just the “tip of the iceberg” of a considerably larger number of serious liver injuries worldwide caused by rivaroxaban.

8.1.7. Conclusion

Rivaroxaban is an oral direct factor Xa inhibitor that has been marketed worldwide since 2008 for the primary and secondary prevention and treatment of thromboembolic disorders. Five years after market launch we are not aware of any published detailed postmarketing case reports of liver injury associated with rivaroxaban. However, liver injury is known under rivaroxaban, labeled adverse reactions include icterus and increased transaminases, alkaline phosphatase, and total and conjugated bilirubin.[87] Of note, the direct thrombin inhibitor ximelagatran was associated with hepatotoxicity during clinical development, which contributed to non-approval by the US FDA, and in other countries marketing was discontinued

after serious cases of liver injury associated with ximelagatran appeared in the postmarketing phase.[175] Looking at premarketing data of rivaroxaban, a published evaluation of rivaroxaban's hepatic events in clinical trials was based on its phase III RECORD studies and included 6131 patients exposed to rivaroxaban. The featured analysis used state of the art eDISH plots[171] and identified ALT increases ≥3x ULN in 2.3% of patients including 9 apparent "Hy's cases" with a simultaneous ≥2x increase in total bilirubin. Further validations concluded that there was only one "true" Hy's case either caused by rivaroxaban or possibly by other incompletely excluded alternate etiologies.[171] A recent systematic review and meta-analysis of premarketing data on liver injury associated with new oral anticoagulants reported ambiguous results. There were a large number of cases with ALT elevations >3x ULN including many with concomitant total bilirubin >2x ULN subsequent to the use of those drugs. At the same time there were no evident risk differences between the individual studied new oral anticoagulants, and a lower risk of such events when compared to low molecular weight heparins.[176] However, safety analyses of clinical trials' data have intrinsic limitations. According to the "Rule of 3" [177,178] the 6131 exposed patients in the RECORD studies are insufficient to reliably detect risks of less than approximately 1:2000, which is typical for idiosyncratic drug-induced liver disease (DILI) but can still be relevant for a drug's overall risk-benefit evaluation.[179] Another limitation is that the duration of treatment in these trials was only 35±2 or 12±2 days, respectively.[171] This is shorter than the currently labeled treatment time for some indications, and 12±2 days are also less than the median latency time of 15.5 days in our case series. Risk factors are another issue of particular interest, as they are often underrepresented in clinical trial populations. Rivaroxaban is often started after orthopedic surgery and many patients concomitantly receive potentially hepatotoxic analgesic drugs. Our series included three patients meeting biochemical criteria of Hy's cases but concomitant use of acetaminophen in therapeutic doses. Dose, long latency time and histology were not compatible with acetaminophen-induced hepatotoxicity in these cases. However, according to current mechanistic concepts acetaminophen in doses below the hepatotoxic threshold may attenuate hepatotoxic "downstream" pathways via glutathione depletion and cytokine-mediated signal transduction. Acetaminophen could therefore have acted as a risk factor for rivaroxaban-induced liver injury.[180,181] Some patients also received metamizole, but hepatotoxicity is not amongst its labeled adverse reactions. Indeed, we found only one case of metamizole-associated liver injury in the literature,[182] but it presented with an allergic skin reaction after short latency, which is different from the pattern observed in our cases. In order to further clarify the causality in our case series, we

planned the conduct of lymphocyte transformation tests (LTT) with in-vitro exposure of lymphocytes from our patients to rivaroxaban. This method has been successfully used for the evaluation of DILI in the past.[183] These planned studies have been delayed because we were unable to obtain rivaroxaban pure substance from the manufacturer of Xarelto®, but we now aim to perform these tests with commercially available rivaroxaban.

Possible mechanisms of rivaroxaban-induced hepatotoxicity are unknown and probably involve complex interactions of several rare factors, possibly also immune-mediated reactions. Of further note, previous studies indicated that rivaroxaban is a shared substrate of the drug transport proteins MDR1 and BCRP, whereas anticoagulant vitamin K antagonists are no strong substrates of MDR1.[184-186] MDR1 inhibitors and loss-of-function BCRP polymorphisms may therefore alter rivaroxaban pharmacokinetics, and further studies may explore the potential role of these factors for rivaroxaban-induced DILI.

The diagnosis of drug-induced liver injury mainly depends on temporal relationship and the exclusion of other causes, which can never be done with absolute certainty. Furthermore, even the widely accepted RUCAM causality scale for DILI has limitations, and discrepancies between expert evaluations vs. standardized scales have been widely discussed and studied.[174,187,188] At least all cases reported to our center were evaluated using senior expertise and the most recognized standardized DILI-specific criteria. In contrast, the routine evaluation of cases that are reported to large pharmacovigilance databases usually lacks detailed case information and sufficient resources for standardized DILI-specific causality assessments. In order to avoid over-interpretation it is therefore reasonable that publicly available search results from those databases only contain the information whether a specific drug is considered as an at least possible cause. Furthermore, we also recognize that some individual cases may have been reported to more than one of the searched databases. Spontaneous reports are neither meant to provide definite proof for the causative role of rivaroxaban in the presented cases, nor can they be used for reliable calculations of quantitative risk estimates. However, we applied the best possible combination of standardized causality assessment plus expert evaluation, and in our long-term experience as a pharmacovigilance center the presented case series of liver injury in association with a newly marketed drug is unusual and reason to raise concern. Premarketing experience and information from international

pharmacovigilance databases are also compatible with the possibility that rivaroxaban continues to cause a considerable absolute number of liver injuries worldwide. In conclusion, we therefore interpret the presented case series as a potentially serious signal that requires follow-up by pharmacoepidemiological cohort studies in suitable databases in order to estimate the absolute and relative risks of serious liver injury associated with rivaroxaban versus alternative anticoagulants.[179] Meanwhile, the apparently rare but potentially serious risk of rivaroxaban-induced liver injury should be considered in the risk-benefit evaluation versus alternative antithrombotic drugs with established safety profiles. In patients treated with rivaroxaban incident symptoms and signs of liver disease should be considered as a potential adverse drug reaction, and if no other likely cause can be identified rivaroxaban should be stopped as soon as possible.

8.2. Allergy-like immediate reactions during the use of herbal remedies as reported in VigiBase®

8.2.1. Authors

Jitka Pokladnikova, Ronald H.B. Meyboom, Ricarda Meincke, David Niedrig, Stefan Russmann

8.2.2. Remarks

Significance for thesis & notable features

This study is not directly related to the prevention of ME in hospitalized patients. However, it contributes to raise awareness of considerable potential risks associated with herbal drugs that are commonly perceived as “safe” and it analyzes reports from the world’s largest international pharmacovigilance database. Risks of allergic reactions towards herbal remedies have to be considered in light of the sometimes very limited evidence for their benefits, especially if used in hospitalized patients with an already high drug and disease burden. This study uses the term adverse drug reaction (ADR) in its pharmacovigilance context as defined by the WHO in 1972.

Contributions of the author of this thesis

David Niedrig contributed to the data analysis and interpretation.

Publication

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8.2.3. Background

There is an increased prevalence in use of herbal medicines among the adult population in many western countries.[189-191] The most recent 2012 US National Health Interview Survey showed that 18% of adults used natural products including herbal medicine during the past 12 months.[191] The public often considers herbal products as safe since they are natural and is unaware that Complementary and Alternative Medicines (CAM) are not tested by regulatory agencies for their safety and efficacy.[192] In most countries, herbal medicines are defined as dietary supplements and as such do not have to meet pre- and post-marketing drug policy regulations.[193] However, use of herbal medicines can be associated with development of severe adverse reactions as a result of complex chemistry of herbals as well as their inappropriate use and a lack of quality control.[194,195] In addition, patients may not disclose self-medication with herbal medicines to their health care professionals, and even if they do there may be limited knowledge of their potential adverse reactions and interactions with concomitantly used prescription drugs.[196,197] In the absence of comprehensive systematic safety evaluations of herbal medicines, spontaneous reporting systems of adverse drug reactions (ADR) play a major role for their worldwide safety surveillance and signal detection.[198] Although there are many case reports of ADR associated with herbals in the literature, the majority of reports are documented in large pharmacovigilance databases, and those valuable resources should be systematically analyzed for ADR associated with herbals.[195,199,200] ADR to herbals cover a wide range of manifestations that are mostly mild and followed by full recovery. However, immediate-type allergic reactions are also a typical, potentially life threatening and therefore clinically most relevant adverse reaction to herbal products.

8.2.4. Objectives

Therefore, we conducted a study that aimed to investigate the reporting patterns and characteristics of immediate allergic adverse reactions associated with herbal medicines in international pharmacovigilance.

8.2.5. Methods

Study settings

VigiBase®, the largest international pharmacovigilance database of spontaneous ADR reports was the source of our reports. VigiBase® is maintained by the Uppsala Monitoring Centre (UMC) in association with the World Health Organization's (WHO)

international pharmacovigilance program. The UMC is an independent foundation and a center for international service and scientific research. It collaborates with 118 member countries around the world that collect and evaluate spontaneous ADR reports.[201] These centers forward anonymized ADR reports received from various primary reporting sources to the UMC in a standardized format, containing structured information on adverse events, involved patients and drugs including standardized semi-quantitative causality assessments.[2]

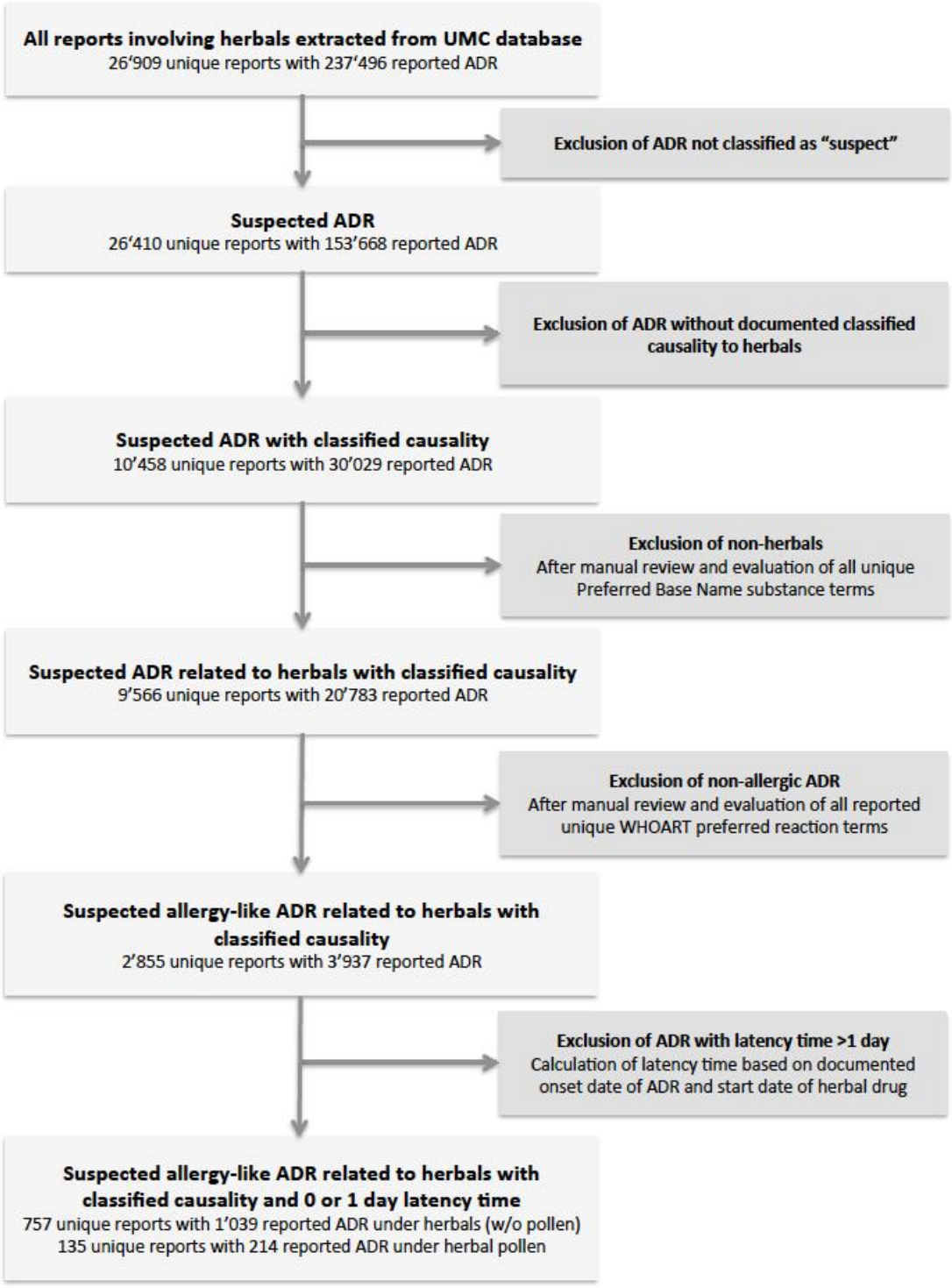
The database of the UMC, Vigibase currently contains over 9 million case reports. The WHO Adverse Drug Reaction Terminology (WHOART) and WHO Drug Dictionary/WHO Herbal Dictionary are used for coding of clinical information in relation to drug therapy and reported drugs on the reports.[201] MedDRA terminology has been made the standard in VigiBase for several years, and there are automated algorithms that convert codes form those two dictionaries in both directions. Herbal medicine refers to herbs, herbal materials, herbal preparations and finished herbal products. Herbal products are assigned herbal anatomical-therapeutic-chemical (HATC) codes specifying their therapeutic use according to the Guidelines for Herbal ATC classification.[202] HATC classification aggregates herbal remedies according to their medical uses that have been found in the literature and does not indicate that the remedy has been proven as effective or safe. Herbal pharmacovigilance terminology is used in accordance with WHO guidelines.[203]

Study design and selection of cases

A flowchart of the study design and case selection process is presented in **Figure 15**. The aim of our study was to focus on immediate-type allergic ADR associated with herbals, because those are potentially life threatening and therefore clinically highly relevant. The level of documentation within VigiBase® is heterogeneous, and it may be difficult to make an exact medical diagnosis based on the available information. With this limitation in mind we defined case selection criteria that are likely indicators of immediate-type allergic reactions (see Table 2 for a listing of included WHOART terms). Because VigiBase® does not allow for a validation of type 1 immediate hypersensitivity reactions according to comprehensive clinical diagnostic criteria we carefully refer to included cases as “allergy-like immediate reactions” in our study. For inclusion in the study population we used the following inclusion criteria: exposure to manually validated herbal products, which must be classified by the primary reporter as “suspect” with regard to the reported ADR; documented causality assessment between herbal product and ADR classified as “possible”, “probable” or “certain”; documented latency time from herbal exposure to

ADR onset of no more than one day; manual selection of WHO-ART preferred terms indicating an ADR that is a likely symptom of an immediate-type hypersensitivity reaction. In contrast, reaction terms that are compatible with but have a low specificity for immediate type allergic reactions such as cough, dyspnea, larynx pain, gastrointestinal symptoms or pruritus were on their own not considered sufficient for inclusion. Furthermore, we excluded ADR associated with the HATC term “herbal pollen not otherwise specified” from the main analysis because these are likely to refer to desensitization vaccines for the treatment of pollen allergies (ADR that may have a distinct special relationship to the indication for the suspected herbal products). ADR were also stratified over asthma-like reactions (defined by WHO-ART preferred terms “asthma”, “stridor” or “bronchospasm”) vs. all other ADR terms with high specificity for immediate-type allergic reactions.

Figure 15: Flowchart of study design and case selection process



Statistical analysis

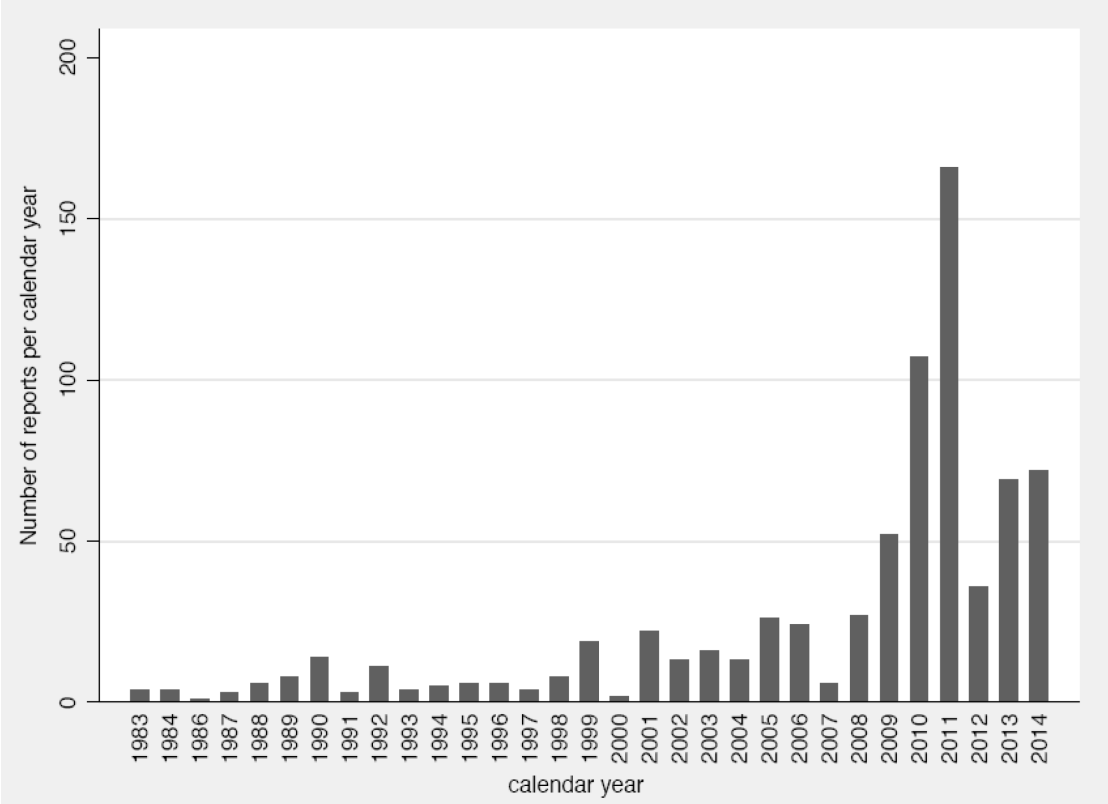
Descriptive statistics was used to analyze case report characteristics. The unexpected ADR to herbals was quantitatively analysed using the Bayesian Confidence Propagation Neural Network methodology (BCPNN), a data-mining technique used for the detection of new signals in spontaneous reporting of ADR.[204] The measure of disproportionality expressed as the Information Component (IC) is used to indicate the frequency of specific drug-ADR combination that occurs more frequently in the database than expected in relation to the number of all reports with the particular drug and ADR and the total number of reports in the database. The IC is a logarithmic measure of association and is calculated as $IC = \log_2 p(x,y) / (p(x) * p(y))$, where: p(x) = probability of a specific drug x is listed on a case report; p(y) = probability of a specific drug-ADR combination x and y is listed on a case report; p(x,y) = probability of a specific drug x is listed on a case report.

An IC of 0 results from drug-ADR combinations for which the number of observed cases is the same as that which might be expected from the overall reporting in the data set. Accordingly, an IC above 0 indicates that a specific drug-ADR combination occurs more frequently in the dataset than expected from the background of the database. For the IC analysis we used the dataset of all reports that met our inclusion criteria and calculated the IC for all specific combinations that occurred with a frequency of 10 or more. Data management and analyses were performed using STATA Version 13.1 (StataCorp LP, College Station, TX, USA).

8.2.6. Results

The initial dataset extracted from VigiBase® comprised 26,909 unique ADR reports with documented exposure to herbal products. These reports were received between 1969 and August 2014. After application of exclusion criteria 757 unique reports remained with 1,039 ADR (more than one reaction term can be reported per case) related to herbal products for the analyses (**Figure 15**). The chronology for receipt of those reports is presented in **Figure 16**, showing a pronounced increase of the reporting frequency in recent years. More than 50% of all included reports came from only three countries, i.e. Germany (22.3%), Australia (14.9%) and Thailand (11.2%). The most frequent primary reporters were physicians (32.1%), followed by hospitals (24.7%) and pharmacists (14.1%)

Figure 16: Number of reports of immediate allergy-like adverse reactions after the use of herbals per year (N=757)



Patients' characteristics

Patient demographics and reporting information of the 757 included reports are presented in **Table 16**. Women were overrepresented among included cases (68.6%), and more than one third of cases fell into the age category from 18 to 44 years.

Table 16: Case report characteristics (N=757)

	n	%
Gender		
Female	519	68.6
Male	225	29.7
Not specified	13	1.7
Age group (years)		
<18	109	14.4
18 - 44	278	36.7
45 - 64	199	26.3
≥ 65	117	15.5
Not specified	54	7.1
Reporting country		
Germany	169	22.3
Australia	113	14.9
Thailand	100	13.2
South Korea	49	6.5
Spain	43	5.7
Sweden	39	5.2
Switzerland	37	4.9
Cuba	29	3.8
United Kingdom	17	2.3
Malaysia	16	2.1
New Zealand	15	2.0
Norway	11	1.5
Other (<10 reports per country)	119	15.7
Reporting source		
Physician	243	32.1
Hospital	187	24.7
Pharmacist	107	14.1
Manufacturer	38	5.0
Consumer / non health professional	14	1.9
Other / not specified	168	22.2

Allergy-like immediate reactions

Characteristics of allergy-like immediate reactions under herbal remedies are presented in **Table 17** along with stratifications over the three given causality categories. The likelihood of a causal connection in the 1,039 reported ADR had been assessed as “possible”, “probable” and “certain” in 59.2%, 32.2% and 8.6%, respectively. Outcome was favorable with recovery in 77.7% of all ADR, and there were no lethal cases. One should note however that there was no information available on the outcome for 9.2%. Asthma-like reactions accounted for only 4.8% of all ADR. The most commonly reported allergy-like immediate adverse reactions associated with herbals were “rash” (16.2%), “urticaria” (15.3%) and “rash erythematous” (13.4%). Anaphylactic and anaphylactoid reactions accounted altogether for 9.5% of reported ADR (anaphylactic reaction 4.5%, anaphylactic shock 2.8%, anaphylactoid reaction 2.2%), and Table 16 shows other serious ADR such as bronchospasm or larynx oedema.

Table 17: Characteristics of immediate allergy-like reactions after the use of herbal remedies (N=757)

	Causality						Overall	
	Possible		Probable		Certain			
	n	%	n	%	n	%	n	%
Total number of reported ADRs [a]	**615**	**59.2**	**335**	**32.2**	**89**	**8.6**	**1039**	**100**
Type of ADRs [a]								
Allergic	584	95.0	319	95.2	86	96.6	989	95.2
Asthma-like [b]	31	5.0	16	4.8	3	3.4	50	4.8
Specification of reported ADRs [a] (WHOART [c] preferred term)								
Rash	108	17.6	53	15.8	7	7.9	168	16.2
Urticaria	86	14.0	57	17.0	16	18.0	159	15.3
Rash erythematous	91	14.8	37	11.0	11	12.4	139	13.4
Allergic reaction	42	6.8	13	3.9	3	3.4	58	5.6
Angioedema	27	4.4	21	6.3	5	5.6	53	5.1
Flushing	29	4.7	15	4.5	4	4.5	48	4.6
Anaphylactic reaction	28	4.6	10	3.0	9	10.1	47	4.5
Face oedema	34	5.5	10	3.0	2	2.3	46	4.4
Rash maculo-papular	23	3.7	21	6.3	-	-	44	4.2
Oedema mouth	14	2.3	14	4.2	10	11.2	38	3.7
Oedema periorbital	24	3.9	9	2.7	3	3.4	36	3.5
Anaphylactic shock	11	1.8	15	4.5	3	3.4	29	2.8
Bronchospasm	14	2.3	11	3.3	1	1.1	26	2.5
Anaphylactoid reaction	11	1.8	8	2.4	4	4.5	23	2.2
Tongue oedema	12	2.0	6	1.8	3	3.4	21	2.0
Asthma	11	1.8	5	1.5	2	2.3	18	1.7
Dermatitis contact	5	0.8	8	2.4	3	3.4	16	1.5
Dermatitis	6	1.0	7	2.1	1	1.1	14	1.4
Oedema pharynx	4	0.7	6	1.8	1	1.1	11	1.1
Oedema generalized	5	0.8	4	1.2	-	-	9	0.9
Eosinophilia	8	1.3	-	-	-	-	8	0.8
Allergy	6	1.0	-	-	1	1.1	7	0.7
Larynx oedema	4	0.7	3	0.9	-	-	7	0.7
Stridor	5	0.8	-	-	-	-	5	0.5
Erythema multiforme	3	0.5	-	-	-	-	3	0.3
Skin reaction localized	2	0.3	-	-	-	-	2	0.2
Bronchospasm aggravated	1	0.2	-	-	-	-	1	0.1
Drug hypersensitivity syndrome	-	-	1	0.3	-	-	1	0.1
Purpura allergic	-	-	1	0.3	-	-	1	0.1
Urticaria acute	1	0.2	-	-	-	-	1	0.1
Outcome								
Recovered	431	70.1	296	88.4	80	89.9	807	77.7
Not recovered (yet)	97	15.8	18	5.4	4	4.5	119	11.5
Recovered with sequelae	10	1.6	7	2.1	-	-	17	1.6
Died	-	-	-	-	-	-	-	-
Unknown / Not specified	77	12.5	14	4.2	5	5.6	96	9.2

[a] ADRs, adverse drug reactions; [b] asthma-like ADRs included WHO-ART preferred terms “asthma,” “stridor” and “bronchospasm,” [c] WHOART, The WHO Adverse Reactions Terminology

Suspect Herbals

Descriptions of specific herbals associated with reported ADR and their route of administration are presented in **Table 18**. Preparations that contained a mixture of several herbals were the suspected cause in 36% of all ADR and therefore by far the most frequently reported herbal products in association with ADR, followed by *Phleum pratense* (common name: *Timothy grass*, 6.5%), *Andrographis paniculata* (several common names including kalmegh, 5.0%), Echinacea purpurea (3.8%) and *Ginkgo biloba* (3.6%). Oral administrations accounted for almost two thirds of ADR, followed by topical / cutaneous and sublingual administrations in 9.0% and 6.4%, respectively.

Table 18: Characteristics of suspect herbals associated with immediate allergy-like reactions (N=757)

	Causality						Overall	
	Possible		Probable		Certain			
	n	%	n	%	n	%	n	%
Total number of reported ADRs [a]	**615**	**59.2**	**335**	**32.2**	**89**	**8.6**	**1039**	**100**
Herbs reported in association with ADRs [a]								
Mixed herbals	220	35.8	126	37.6	28	31.5	374	36.0
Phleum pratense	16	2.6	25	7.5	27	30.3	68	6.5
Andrographis paniculata	27	4.4	25	7.5	-	-	52	5.0
Echinacea purpurea	30	4.9	6	1.8	3	3.4	39	3.8
Ginkgo biloba	29	4.7	6	1.8	2	2.3	37	3.6
Hedera helix	25	4.1	4	1.2	1	1.1	30	2.9
Plantago ovata	6	1.0	9	2.7	4	4.5	19	1.8
Hypericum perforatum	13	2.1	4	1.2	1	1.1	18	1.7
Viscum album	13	2.1	4	1.2	1	1.1	18	1.7
Valeriana officinalis	10	1.6	6	1.8	1	1.1	17	1.6
Cimicifuga racemosa	11	1.8	5	1.5	-	-	16	1.5
Mentha x piperita	6	1.0	9	2.7	1	1.1	16	1.5
Other (<15 ADRs per herbal)	209	34.0	106	34.0	20	22.5	335	32.2
Administration route of reported herbal								
Oral	394	64.1	234	69.9	29	32.6	657	63.2
Topical / cutaneous	57	9.3	26	7.8	10	11.2	93	9.0
Sublingual	18	2.9	21	6.3	27	30.3	66	6.4
Intravenous	29	4.7	6	1.8	4	4.5	39	3.8
Subcutaneous	11	1.8	12	3.6	6	6.7	29	2.8
Other (≤10 ADRs per route)	38	6.2	14	4.2	6	6.7	58	5.6
Not specified	68	11.1	22	6.6	7	7.9	97	9.3

[a] ADRs, adverse drug reactions

Disproportionality analysis

Calculations of IC values for all 16 specific herbal / allergy-like reaction combinations that had been reported at least 10 times are presented in **Table 19**. Accordingly, significantly higher frequencies than expected by chance were found for *Phleum pratense* (Timothy grass) linked to oedema of the mouth (IC= 1.81, 95%CI 0.67-2.86) and to anaphylactic reactions (IC= 1.23, 95%CI 0.03-2.33).

Table 19: Most frequently reported (N≥10) specific combinations of herbal remedies and allergic reactions with their IC values

Herbal remedy	WHOART [b] preferred term	N reports	%	IC [a]	(95% CI)
Mixed herbals	Rash	75	(7.2)	-0.15	(-0.60 - 0.30)
Mixed herbals	Urticaria	58	(5.6)	-0.44	(-0.93 - 0.04)
Mixed herbals	Rash erythematous	36	(3.5)	-0.93	(-1.53 - -0.36)
Mixed herbals	Face oedema	21	(2.0)	-0.11	(-0.95 - 0.68)
Mixed herbals	Allergic reaction	20	(1.9)	-0.52	(-1.35 - 0.26)
Mixed herbals	Rash maculo-papular	20	(1.9)	-0.12	(-0.98 - 0.70)
Mixed herbals	Oedema mouth	19	(1.8)	0.02	(-0.88 - 0.87)
Mixed herbals	Anaphylactic reaction	15	(1.4)	-0.63	(-1.59 - 0.26)
Mixed herbals	Angioedema	15	(1.4)	-0.80	(-1.76 - 0.07)
Mixed herbals	Flushing	15	(1.4)	-0.66	(-1.62 - 0.22)
Mixed herbals	Anaphylactoid reaction	12	(1.2)	0.08	(-1.08 - 1.16)
Phleum pratense	Oedema mouth	12	(1.2)	**1.81**	**(0.67 - 2.86)**
Andrographis paniculata	Urticaria	11	(1.1)	0.01	(-1.11 - 1.01)
Mixed herbals	Oedema periorbital	11	(1.0)	-0.69	(-1.83 - 0.33)
Mixed herbals	Anaphylactic shock	10	(1.0)	-0.52	(-1.74 - 0.58)
Phleum pratense	Anaphylactic reaction	10	(1.0)	**1.24**	**(0.03 - 2.33)**

[a] IC, information component; [b] WHOART, The WHO Adverse Reactions Terminology

8.2.7. Conclusion

We report on a series of 757 case-reports indicative of allergy-like adverse reactions during the use of herbal remedies from the Vigibase of spontaneous ADR reports coming from 42 countries since 1969. Our study documents that a large number of different herbal remedies cause immediate allergy-like reactions in the population. Among all reports, mixed herbals, *Phleum pratense* and *Andrographis paniculata* were most frequently reported in association with ADR. *Andrographis paniculata* is well known in Ayurveda medicine and typically used for the treatment of common cold. Previously reported findings from Thailand investigating the safety of *Andrographis paniculata* showed a similar range of hypersensitivity reactions ranging from skin reactions to anaphylaxis.[205] Case-reports indicative of hypersensitivity to other most frequently reported herbals in our study have been published previously.[206-211]

High proportion of reports concerned women between the age of 18 and 44. The most frequently reported manifestations of allergy-like immediate reactions were skin reactions, and also anaphylactic / anaphylactoid reactions most frequently observed after oral administration. Such severe ADR are rarely seen after oral use of herbals. The occurrence of allergic reactions is rather more likely to be expected after cutaneous and mucosal exposure, a known risk factor for sensitization to allergens. It is reasonable to assume that rather easy to diagnose reactions with a short time to onset and skin manifestations as well as serious reactions are more frequently reported compared to other reactions. Oral administration of herbals in females may be most common in the population. Such observation is often made in CAM/herbal use prevalence studies.[189-191] It is therefore expected that this population is also overrepresented in all included reports. A higher reporting rate of ADR by females could be another factor contributing to such pattern.[212] On the other hand, a higher proportion of females experiencing an adverse reaction in our study may confirm results of other studies where a higher incidence of hypersensitivity reaction in females compared to males was found.[213,214] Nevertheless, this finding does not allow conclusions regarding the role of those characteristics as risk factors although they are further discussed in the literature.

Asthma-like reactions were found in 4.8% of reports. Some commonly used herbals display a wide spectrum of cross-reactivity to other common inhalation or food allergens. Therefore a preexisting diagnosis of asthma and other atopic diseases may be a risk factor for the development of allergic reactions to herbals. There is a relevant incidence of herbal use among patients with known allergies.[215] For example, herbal medicine was shown to be the third popular choice among patients

suffering from asthma with a prevalence of 60-70% in patients with a history of moderate or severe asthma in the United Kingdom.[216] These findings imply that in the presence of known atopic diseases health professionals and patients should only use herbals with great care in order to prevent severe allergic reactions to herbals in this special population. Other relevant factors that were not recorded and could have contributed to the development of allergy-like reactions could have been user's genetics, nutrition status, concurrent medication, disease states (e.g.: food allergies) and exercise induced anaphylaxis. Also, unrecognized herbal-drug interactions could result in a lack of allergy control and manifestation of allergy symptoms.

Strengths of our study include the international collection of reports from 42 countries over more than four decades and the use of standardized HATC drug classification, WHOART nomenclature and formal causality assessment for adverse reactions. At the same time it is important to recognize special characteristics and inherent limitations of this data source for the study design and interpretation of findings. Most important, spontaneous reporting data do not provide information on the actual exposure to herbals in a population or on the incidence of related ADR. Therefore, qualitative descriptive analyses and signal detection for previously unknown drug safety issues are the primary strength of spontaneous reporting systems rather than quantitative analyses. Furthermore, the level of documentation in VigiBase® is heterogeneous, the extracted reports do not contain original detailed free-text descriptions by the primary reporters, and particularly for early reports formal causality assessment may not be available requiring exclusion from our study population. One must also realize that a standardized reaction term has many advantages, but it is not the same as a clinical diagnosis based on established clinical diagnostic criteria.[217] In light of those limitations we used a restrictive study design emphasizing high specificity with regard to the likely diagnosis of immediate-type allergic reactions and consequently excluded the majority of reports from the extracted original raw dataset. Such a conservative approach implies reduced sensitivity for signal detection, but we believe that overall it improves the interpretability of our findings. There are several other challenges that pharmacovigilance studies investigating risks associated with herbal remedies face in general. As a result of insufficient herbal product regulations, some ADR may be attributable to a lack of standardization, contamination, adulteration, plant misidentification/substitution, improper use of herbal medicines including their inappropriate labeling rather than pharmacological/toxicology effects of herbals.[193-195,218] Also, implementation of innovative preparation methods of traditionally used herbal remedies may alter pharmacological/toxicological properties of herbs and lead

to their toxicity rather than therapeutic use. In the era of market globalization, the knowledge of traditional preparation and use of herbals is therefore necessary given the increase in use of traditional herbal remedies outside of their culture of origin.
An estimate of the frequency of ADR to herbals is not possible based on analyses of spontaneous reporting data, but we must assume that our findings represent only the "tip of the iceberg" regarding safety issues with herbal remedies.[198] Moreover, underreporting of adverse events particularly herbals by patients as well as health care professionals is high and health care professionals are not always aware of potential safety issues associated with herbal use.[196-198,219,220]
In summary, any pharmacologically active product including herbal has the potential to cause harm. We found that herbal medicines for oral use carry a risk for allergy-like immediate ADR and that studies using the WHO-UMC pharmacovigilance database can identify specific associations between particular herbals and adverse reactions. As the prevalence of herbal use is increasing, health care professionals as well as patients need to become better informed about the possible risks associated with herbal medicines. When health care professionals take drug histories they should actively ask their patients also about all self-administered herbal remedies and dietary supplements. Further studies are needed to establish associations and risk factors that are related to herbal use and allergic reactions.

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